Amsterdam, 18 October 2019
EMA/595311/2019

Withdrawal Assessment report

Nuzyra (omadacycline tosylate)

Procedure No. EMEA/H/C/4715

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Abbreviations

ABSSSI	Acute bacterial skin and skin structure infections
AC	Alveolar cell
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Action potential
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
ATCC	American Type Culture Collection
ATS	American Thoracic Society
AUC	Area Under Curve
B/R	Benefit/Risk
BAL	Bronchiolar lavage
BBB	Blood brain barrier
BCS	Biopharmaceutics Classification System
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CABP	Community-acquired bacterial pneumonia
CAP	Community Acquired Pneumonia
CE	Clinically evaluable
CEP	Certificate of suitability of Monographs of the European Pharmacopoeia
CF	Cystic fibrosis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
CLr	Renal clearance
CLSI	Clinical & Laboratory Standards Institute
Cmax	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance
CSR	Clinical study report
cSSSI	Complicated skin and skin structure infections
CT	Computed tomography
CV	Coefficient of variation
CYP	Cytochrome P450
DBL	Database lock
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECR	Early Clinical Response
EDTA	Ethylenediaminetetraacetic acid
ELF	Epithelial lining fluid
EMA	European Medicines Agency
EOT	End of treatment
ESBL	Extended-spectrum beta-lactamase
ESRD	End-stage renal disease
EU	European Union

EUCAST	European Committee on Antimicrobial Susceptibility Testing
FCC	Food Chemicals Codex
FDA	Food and Drug Administration
FIC	Fractional inhibitory concentrations
FK	Karl Fisher
FTIR	Fourier-Transform Infrared Spectroscopy
G-	Gram negative
G+	Gram positive
GCP	Good Clinical Practice
GCP	Gas Chromatography
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAP	Hospital-acquired pneumonia
HCAP	Health-care associated pneumonia
HDPE	High-density polyethylene
HPLC	High-performance liquid chromatography
HPLC-UV	High-performance liquid chromatography - Ultraviolet
HR	Heart rate
IACR	Investigator's assessment of clinical response
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
INN	International non-proprietary name
ITT	Intention to treat
IV	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometric detection
LDPE	Low-density polyethylene
LLOQ	Lower Limit of Quantification
LoQ	List of Questions
MAA	Marketing authorisation application
MDR	Multi-drug resistance
MDRSP	Multidrug-resistant *S. pneumoniae*
ME	Microbiologically-Evaluable
MIC	Minimum Inhibitory Concentration
MIC50	Minimum inhibitory concentration against 50% of the isolates
MIC90	Minimum inhibitory concentration against 90% of the isolates
Micro-mITT	Microbiological modified intent-to-treat
MIEC	Minimal inhibitory extracellular concentration
mITT	Modified intent to treat
MO	Major Objection
MOA	Monoamine oxidase
MRSA	Methicillin resistant Staphylococcus aureus
MSSA	Methicillin susceptible Staphylococcus aureus
MTD	Maximum tolerated dose
N/A	Not Applicable

ND	Not determined
NDA	New Drug Application
NF	National Formulary
NMR	Nuclear magnetic resonance
NRU	Neutral Red Uptake
OC	Other Concern
OMC	Omadacycline
PD	Pharmacodynamic
PEC	Predicted environmental concentration
Ph. Eur.	European Pharmacopoeia
PI	Product information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PL	Product leaflet
PO	Per oral
popPK	Population pharmacokinetics
PORT	Pneumonia Outcomes Research Team
PRAC	Pharmacovigilance Risk Assessment Committee
PRSP	Penicillin resistant Streptococcus pneumoniae
PSSP	Penicillin susceptible Streptococcus pneumoniae
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTA	Probability of Target Attainment
PTE	Post-therapy evaluation
PXR	Pregnane X receptor
q.s.	quantity sufficient
q12h	Every 12 hours
q24h	Every 24 hours
QD	Four times daily
RBC	Red blood cell
RHD	Recommended human dose
RMP	Risk Management Plan
ROI	Residue on Ignition
SAE	Serious adverse event
SAP	Statistical analysis plan
SB	Single blind
SBP	Systolic blood pressure
SEM	Structural equation modeling
SIR	Systemic inflammatory response
SIRS	Systemic inflammatory response syndrome
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPN	Streptococcus pneumoniae
t1/2	Terminal half-life
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TK	Toxicokinetic
TK	Time-kill

tmax	Time of maximum plasma concentration
TOC	Test of cure
ULOQ	Upper limit of quantitation
US	United States
USP	United States Pharmacopeia
uUTI	Uncomplicated urinary tract infection
V	Volume of distribution
VAP	Ventilator-acquired pneumonia
WBC	White blood cell
VPC	Visual predictive check
VRE	Vancomycin-resistant enterococci
VSE	Vancomycin-susceptible enterococci
Vss	Steady-state volume of distribution
XRPD	X-ray powder diffraction

1. CHMP Recommendation

Based on the review of the data on quality, safety, efficacy, the application for Nuzyra (previously proposed named Nualto) in the treatment of adults with the following infections (see sections 4.4 and 5.1):

- Community-acquired pneumonia (CAP)

- Acute bacterial skin and skin structure infections (ABSSSI)

is not approvable since a "major objection" has been identified, which preclude a recommendation for marketing authorisation at the present time. The details of this major objection are provided in the List of Questions.

The major objection precluding a recommendation of marketing authorisation pertains to the following principal deficiencies:

Benefit/Risk

A positive B/R balance for omadacycline in CAP cannot be inferred based on available data. The evidence for this indication comes solely from a single pivotal study. Moreover, an unexplained difference in mortality rate was noted between treatment arms, enhancing the uncertainties due to the single pivotal trial. Additional efficacy and safety data from the planned further study in CAP will be required to provide a comprehensive basis for evaluating the B/R balance for omadacycline in CAP, for the purposes of authorisation for this indication.

Inspection issues

GMP inspection

Inspections of the drug substance manufacturing site and/or the drug product manufacturing site and/or the batch release site are not considered necessary for finalization of assessment of Module3.

GCP inspection

A routine request for GCP inspection was adopted by CHMP for the following clinical studies: PTK0796-ABSI-1108 and PTK0796-CABP-1200 (ref INS/GCP/2018/031). The routine inspection included one site for each of the studies (located in Poland and South Africa) plus the contract research organisation. In summary, the conclusion was that the clinical trial data are reliable enough to support the application submitted for Nuzyra.

New active substance status

Based on the review of data on the quality of the active substance, the Rapporteur considers that omadacycline is to be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

2.1.1. **Disease or condition**

The indications applied for are treatment of adults with:

- Acute bacterial skin and skin structure infections (ABSSSI)
- Community-acquired bacterial pneumonia (CABP)

2.1.2. **Epidemiology**

Acute bacterial skin and skin structure infections (ABSSSI) can be serious, limb- or life-threatening conditions, often requiring systemic antibiotic therapy and possibly surgical management and hospitalisation. In 2012, there were an estimated 850,000 skin infections across the 5 major EU markets (France, Germany, Italy, Spain, and United Kingdom). The economic impact of CAP is substantial, with an annual cost in excess of $10 billion in Europe.

Community-acquired pneumonia is the most common infectious disease leading to hospitalisation and mortality among all age groups and is a leading cause of morbidity and mortality and throughout the world. The annual incidence of CAP across Europe ranges from 1.54 to 1.7 per 1,000 adults with over 3 million ambulatory cases and approximately 1 million hospital admissions per year. Mortality rates are 5% to 15% in hospitalised patients. Between 1.2% and 10% of adults admitted to hospital with CABP are managed in an intensive care unit, and for these patients mortality is more than 40%. Even after successful treatment, residual symptoms such as cough, chest pain and fatigue may persist for up to 6 months.

2.1.3. **Aetiology and pathogenesis**

Gram-positive bacteria, especially *S. aureus* and *Streptococcus* spp., are the most frequent cause of ABSSSI. Patients with necrotising skin infections, infections associated with human or animal bites, traumatic or surgical wound infections, and skin infections associated with iv drug use, as well as immunosuppressed patients with ABSSSI, may require treatment with antibiotics that provide more than narrow spectrum anti-staphylococcal and anti-streptococcal activity.

Typical bacterial pathogens implicated in the majority of cases of CABP are *S. pneumoniae* and *Haemophilus influenzae*. Atypical pathogens, including *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae*, affect a considerable proportion of CABP patients.

2.1.4. **Clinical presentation, diagnosis**

ABSSSI comprises several types, including cellulitis/erysipelas, major abscess and wound infection, as well as rarer conditions such as infected lower extremity ulcers. In some instances, ABSSSI may arise related to a foreign body, animal or human bite, trauma or surgical wound, or iv drug abuse, while in others no obvious cause may be found. Patients with pre-existing immunosuppression or diabetes mellitus may be more prone to ABSSSI.

Pneumonia may present in different ways in different patients, ranging from mild symptoms of lower respiratory tract infection, with or without fever, to severe sepsis and systemic collapse. CABP is classified separately from Hospital-acquired pneumonia (HAP) (developing ≥48 hours after hospital admission), Ventilator-acquired pneumonia (VAP) or Health-care associated pneumonia (HCAP), which

develop in hospitalised and ventilated patients or residents of long term care facilities, tend to be caused by a different range of pathogens, in particular a higher frequency of multi-drug resistant organisms, and are associated with increasing morbidity and mortality.

2.1.5. **Management**

The management of ABSSSI includes topical and/or systemic antibiotics generally aimed at Gram positive pathogens (including beta-lactams, lipopeptides, oxazolidinones, glycopeptides and tetracyclines), combined with other topical treatments and dressings, and often with adjunctive surgical management to remove any causative foreign body, debride diseased tissue and drain any associated collection. Addition of a further antibiotic with a different profile may be required where Gram negative or anaerobic pathogens are suspected.

The management of CABP includes systemic antibiotics (including beta-lactams, macrolides, fluoroquinolones, oxazolidinones and tetracyclines), combined with supportive care e.g. fluid management, supplementary oxygen, ventilatory support and, occasionally, adjunctive procedures e.g. drainage of an associated pleural effusion. Empiric therapy, expected to cover the most common organisms and most common resistance patterns for the local area, may be indicated where a causative pathogen cannot be identified from microbiological samples. Only fluoroquinolones, macrolides and tetracyclines provide reliable cover where atypical pathogens are suspected or confirmed.

The emergence of resistance, including multi-drug resistance (MDR), against first line antibiotics has, as in other areas, made treatment of both ABSSSI and CABP more challenging and there is an unmet need for additional antibiotic treatment options.

2.2. About the product

Omadacycline exhibits a bacteriostatic effect by binding to the 30S subunit of the bacterial ribosome, thereby blocking bacterial protein synthesis.

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code not yet assigned.

The proposed indication is:

Omadacycline is indicated for the treatment of adults with the following infections:

- Community acquired bacterial pneumonia (CABP)
- Acute bacterial skin and skin structure infections (ABSSSI)

The proposed posology is:

CAP and ABSSSI: Treatment duration is 7 to 14 days.

Infection	**Loading Doses**	**Maintenance Dose**
CAP	Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice	100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily

ABSSSI	Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice OR Day 1 and Day 2: 450 mg orally once daily	100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily

Hepatic or Renal Impairment

No dose adjustment is necessary in patients with mild, moderate, or severe hepatic impairment (Child Pugh classes A, B, or C) (see section 5.2).

No dose adjustment is necessary in patients with mild, moderate, or severe renal impairment (including End Stage Renal Disease) (see section 5.2).

2.3. The development programme/compliance with CHMP guidance/scientific advice

The applicant sought scientific advice on the overall development programme for acute bacterial skin and skin structure infections (ABSSSI) and complicated skin and skin structure infections (cSSSI), community-acquired bacterial pneumonia (CABP), from national agencies (FR, UK, DE) and CHMP in 2008 and 2009.

A US pivotal Phase 3 study in cSSSI was initiated but then discontinued by the applicant following a change in FDA Guidance on the development of treatments for ABSSSI. A planned EU pivotal study in cSSSI was subsequently delayed. The applicant later sought advice from CHMP on the design of new Phase 3 studies in ABSSSI and CABP in 2015 in two parallel procedures.

Scientific advice was generally consistent between CHMP and FDA, with the exception of primary efficacy endpoint timing in Phase 3 clinical studies (Post-Treatment Evaluation (PTE) for CHMP, Early Clinical Response (ECR) for FDA), which was addressed by separate Statistical Analysis Plans.

2.4. General comments on compliance with GMP, GLP, GCP

No specific concerns had been identified by the assessment at the time of adoption of the inspection request. Critical observations raised at a site in study 16301, identified by the sponsor and reported in the FDA NDA, led to exclusion of data from this site for the purposes FDA analysis, as highlighted at D120. According to the FDA NDA assessment, a sensitivity analysis excluding the patients from this site was consistent with the results from primary analysis.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

New active substance status
Based on the review of data on the quality of the active substance, the Rapporteur considers that omadacycline is to be qualified as a new active substance in itself.

Orphan designation - Not Applicable

Similarity with orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0269/2018 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0269/2018 was not yet completed as some measures were deferred.

3. Scientific overview and discussion

3.1. Quality aspects

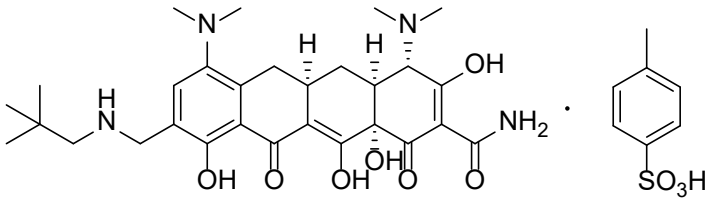
3.1.1. Introduction

Nuzyra (omadacycline) has been developed in two dosage forms, powder for concentrate for solution for infusion (IV product) and film-coated tablets (oral tablets).

3.1.2. Active Substance

General Information

The International non-proprietary name (INN) is omadacycline and the salt form omadacycline tosylate is the drug substance. The drug substance is a crystalline compound with three forms, Form 3 being the desired polymorphic form. Aqueous solubility of the drug substance is highly soluble across the pH range 1-7, with a solubility of ≥ 2 g/mL for all tested solutions.



Molecular formula:	Salt form on anhydrous basis: $C_{29}H_{40}N_4O_7 \cdot C_7H_8O_3S$
Relative molecular mass:	Salt form: 728.9

Manufacture, process controls and characterisation

The synthesis of omadacycline tosylate was developed and is sufficiently robust to provide assurance that the process produces the drug substance of consistent quality, complying with the designed specification.

Starting materials

The starting material was agreed through the pre-submission MAA meetings advice with the Co-Rapporteur on 03-May-2018 (reference is being made to the Co-Rapporteur meeting minutes) and the Rapporteur on 08-Jun-2018 (reference is being made to the Rapporteur meeting minutes) and supported by CHMP.

Intermediate

There are intermediates defined in the omadacycline tosylate drug substance process.
The route of synthesis is sufficiently described, and the major phases in the synthesis of omadacycline tosylate are controlled during the reaction.

Characterisation

The structure of Omadacycline *p*-Toluenesulfonate (omadacycline tosylate) drug substance has been confirmed through Fourier-Transform Infrared Spectroscopy (FTIR), UV, Mass Spectrum, NMR (including multiplicity, coupling constants and integral values), and X-ray Crystallography. In addition, Structure and XRPD were used to confirm Form 3 of the tosylate salt.

Impurities

Potential organic related substances and degradants are detected using stability indicating HPLC methods.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The specifications for the drug substance are based on batch analyses of several batches of drug substance prepared by the commercial process, and batches used clinically and toxicologically, as well as stability data. The methodology has been validated to meet the general requirements of Ph Eur (where relevant) and the ICH guideline Q2B, Validation of Analytical Procedures; Methodology.

Omadacycline *p*-toluenesulfonate (omadacycline tosylate) drug substance is packaged in an appropriate container closure system. The specification is considered acceptable.

Stability

Stability data are available for 3 primary registration/stability batches of omadacycline tosylate drug substance through 18 months at long term conditions and 6 months at accelerated conditions. The results through 18 months at long term conditions and 6 months at accelerated conditions are consistent, remain unchanged and meet the acceptance criteria for appearance, polymorphic form, water, assay and related substances. Individual data are presented indicate that the drug substance is stable at the intended storage condition, refrigeration (2°C to 8°C). The stability data provided support the retest period of 24 months when stored below 2°C to 8°C provided that the issues identified have been clarified.

3.1.3. Finished Medicinal Product - Powder for Concentrate for Solution for Infusion

Description of the product and Pharmaceutical Development

Omadacycline 100 mg Powder for Concentrate for Solution for Infusion is a sterilized, lyophilized powder reconstituted to a solution for infusion. It is available as a 100 mg unit dose in a clear glass vial with grey elastomer stopper, and aluminium crimped-on seal with tear-off cap.

The compatibility of the chosen excipients with omadacycline has been demonstrated by in use stability of reconstituted lyophilizate and solid-state drug product stability studies. The final formula consists of

omadacycline tosylate, sucrose, hydrochloric acid concentrated, sodium hydroxide and water for injection. The container closure system (clear glass vial with a grey elastomer stopper, secured with aluminium crimped-on seal with a tear-off cap) is also in common use for packaging of commercial sterile pharmaceutical products and meets USP/Ph. Eur. requirements. The pharmaceutical development has adequately been described and it is considered to be acceptable. The choice of sterile processing has been justified.

Manufacture of the product and process controls

The process for the manufacturing of the finished product follows conventional pharmaceutical practices.

It is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product 100 mg powder for solution for infusion of consistent quality, complying with the designed specification.

Product specification, analytical procedures, batch analysis

The release and stability (shelf-life) specifications presented cover relevant parameters for the dosage form: appearance , identification, assay, related substances, visible particles of the reconstituted solution, sub-visible particles of the reconstituted solution, uniformity of dosage units, osmolality of the reconstituted solution, pH of the reconstituted solution, water content, bacterial endotoxins, sterility. The methodology is validated to meet the general requirements of Ph Eur (where relevant) and the ICH guideline Q2B, Validation of Analytical Procedures; Methodology.

Stability of the product

Stability data for omadacycline IV was provided and support the proposed shelf life. The results provided through 24 months at long term conditions and 6 months at accelerated conditions support the proposed shelf-life provided and the issues identified have been clarified by the applicant.

3.1.4. Finished Medicinal Product – Film-coated tablets

Description of the product and Pharmaceutical Development

The drug product is described as an immediate release, yellow-coloured, diamond-shaped, film-coated tablet containing the drub substance omadacycline tosylate equivalent to 150 mg of omadacycline.

All excipients utilized to manufacture omadacycline tablets are commonly used in pharmaceutical applications. The dissolution method development has been provided. The dissolution conditions are justified.

The final tablet to be proposed for the commercial market is a yellow, diamond shaped, film-coated tablet with “OMC” on one side and “150” on the other side.

The manufacturing process development has been described in detail. The process of manufacture is a standard process. The conditions setting, and in-process controls have been discussed.

Microbial testing on one batch per year on release as proposed by the applicant is considered justified. No changes in microbial growth have been observed up to date.

Manufacture of the product and process controls

The process is considered a standard manufacturing process and robustness of the process have been demonstrated during development.

Product specification, analytical procedures, batch analysis

The release and stability (shelf-life) specifications presented cover relevant parameters for the dosage form: appearance, identification, assay, related substances, dissolution, water content, uniformity of dosage units, microbial enumeration, sodium bisulphite identification.

A risk assessment with respect to the potential presence of elemental impurities in the drug product based on the general principles outlined in Section 5.1 of ICH-guideline Q3D has been performed.

The analytical methods have been described and summary of validation is presented in alignment with the general requirements of Ph Eur (where relevant) and the ICH guideline Q2B, Validation of Analytical Procedures; Methodology. Microbiological examination test is performed according to the methods described in European Pharmacopeia 2.6.12 and 2.6.13.

Batch analysis results comply with the proposed specification and confirm that batches are of consistent quality.

The proposed commercial packaging is an aluminium blister with an integrated desiccant and aluminium lidding blister. The packaging materials have been adequately described.

Stability of the product

Updated long term stability data is presented through 18 months at long term conditions. The data remains consistent and meets the acceptance criteria for appearance, assay, related substances, dissolution and water content.

Based on the stability data, the shelf life and storage condition proposed by the applicant is judged acceptable.

Adventitious agents – *N/A*

GMO – *N/A*

3.1.5. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The information provided on drug substance and drug product is considered sufficient.

The choice of aseptic process has been justified.

The application is recommended for approval from a chemical and pharmaceutical point of view.

3.2. Non-clinical aspects

3.2.1. Pharmacology

Primary pharmacodynamics – see section 3.3.2. Pharmacodynamics.

Secondary pharmacodynamics

Potential off-target effects of omadacycline was evaluated in batteries of receptors and ion channels. Omadacycline was found to inhibit the muscarinic M2 receptor, with an IC50 value of 4.25 µM. In addition, IC50 values between 10 and 30 µM were found in nine binding assays (adenosine 3 receptor, alpha 2 adrenergic 2B receptor, dopamine D3 receptor, histamine H3 receptor, muscarinic M1 receptor, opiate delta receptor, serotonin transporter, serotonin 5HT3 ion channel, pregnane X receptor (PXR)).

Safety pharmacology

In vitro studies

In general, omadacycline caused depolarisation of the resting membrane potential, reduced AP amplitude, slight AP prolongation, reduced upstroke and rate of depolarisation at concentrations >100 µM, indicating low clinical relevance.

Omadacycline was considered a low-potency blocker of hERG K+ current (IC25 166 µg/mL) and INa (IC50 1.5 mM). Omadacycline inhibited the Na+/K+ ATPase pump current at approximately 10-fold lower concentrations (IC50 of 0.29-0.52 mM) than those that affected hERG K+ and INa. Thus, the observed effects on hERG K+ and INa could be secondary to depolarization of the resting potential. Due to exposure margins of ≥ 97, these findings are considered of low clinical relevance.

In the rabbit SA-node, increased cycle length and reduced spontaneous beating rate induced by the pan-muscarinic M2 agonist carbamylcholine was reversed by omadacycline concentrations of 8-390 µM. This is consistent with omadacycline being a muscarinic M2 antagonist, with an IC50 value of 4.25 µM, and may indicate a potential to inhibit vagal regulation of the SA node.

In vivo studies

In anaesthetized monkeys, omadacycline led to decreased dP/dtmax+, dP/dtmax-, and left ventricular dP/dt.P-1 in the first 15-60 minutes of omadacycline infusion at the highest dose of 90 mg/kg (14 times the clinical relevant AUC).

In conscious monkeys, omadacycline resulted in a slight increase in blood pressure (systolic, diastolic and mean) and a moderate increase in heart rate at all dose levels (increased with 37, 58, and 27 BPM at 5, 20 and 40 mg/kg, respectively). While blood pressure normalized within 30 minutes, the increase in heart rate persisted for ≥ 4.5 hours post-dose initiation. The findings were consistent with M2 antagonist activity seen in binding assays, and with reversal of M2 agonism effects (i.e., reduced spontaneous beat rate) in the rabbit sinoatrial node study in vitro. No effects were seen on ECG parameters, body temperature, or pulmonary/respiratory parameters.

No omadacycline-related effects were seen on renal parameters in rats. In a seizure threshold study in rats, omadacycline had a small anticonvulsive effect at 25 and 50 mg/kg. No effects were seen on locomotor activity in an Irwin test in rats. A significant increase in latency to pain response was seen in high-dose animals (50 mg/kg) at 0.5 and 24 hour time points. The range of individual responses was however wide and overlapped with data in the control and other treated groups, and the importance of this finding is unclear.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions were evaluated.

3.2.2. **Pharmacokinetics**

Methods of analysis

The liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods used for bioanalysis are considered adequately validated, with acceptable selectivity, calibration ranges, accuracy and precision. Precision and accuracy were within the acceptable limits for the dilution, indicating that samples above the ULOQ (upper limit of quantitation) can be accurately quantified by diluting with control plasma to a concentration within the range of the calibration curve.

Absorption

In vitro data indicate that omadacycline can be classified as a poor passive permeability compound, and a substrate for P-gp transport across Caco-2 monolayers, which is likely to limit the overall omadacycline absorption and, in particular, distribution to tissues with a high P-gp expression.

After single-dose IV administration, plasma exposure was dose-related and plasma elimination linear, with short terminal elimination disposition half-lives in mice and rats (2.0 to 5.5 hours in mice and 3.5 to 5.7 hours in rats), and longer in monkeys (14 to 21 hours). Correspondingly, higher clearance was observed in mice and rats (0.9-1.2 L/h/kg) than in monkeys (0.3 L/h/kg). Steady-state volume of distribution (Vss) was similar across species (3-7 L/kg). After oral administration, Cmax was reached in 0.5-3 hours and 2-4 hours in rats and monkeys respectively.

Oral absorption was low in rats (2.9 to 4.2% in plasma and blood respectively), and an absolute oral bioavailability was as low as 0.2 % in fasted animals, slightly higher in non-fasted animals. Based on total recovery of radioactivity, total absorption has been re-estimated to about 0.5%. This low bioavailability may be due to an interaction with bile salts in the rat intestine (Lin et al, Antimicrob Agents Chemother 61:e01784-16 https://doi.org/10.1128/AAC.01784-16).

Low plasma exposure levels were also achieved in monkeys following PO administration of omadacycline as HCl salt and as tosylate salt. There were no differences in PK parameters between the male and female monkeys, or between salt forms. In humans, bioavailability is around 35 %.

Based on TK data from repeat-dose IV toxicity studies, Cmax and AUC levels increase in a dose-related manner in rats and monkeys, without sex-related differences in exposure. There were no significant accumulation with repeat daily dosing up to 13 weeks (accumulation ratios <1.8). After oral administration, systemic exposures were lower but displayed similar characteristics.

Distribution

Omadacycline (10-10 000 ng/mL) exhibited low binding to plasma proteins in plasma from mouse, rat, monkey, and human (15-21%), with no major species differences.

Distribution data indicate that omadacycline is rapidly and widely distributed following both IV and PO administration in pigmented and albino male rats, with levels above blood levels in most tissues, including lung and skin. At 24h post IV dose, highest levels indicating tissue retention were seen in bone mineral, Harderian gland and thyroid gland. After PO administration, highest levels were observed in bone mineral, liver, GI-tract, spleen, Harderian gland and salivary gland. Low levels in the CNS indicate limited distribution across the BBB. At 24h post-dose, uveal tract levels were not measurable, indicating lack of retention to melanin. While very high levels were seen in bile 5 minutes after IV administration, the levels at 24h were not measurable. Distribution to female reproductive organs (including trans-placental) has not been addressed but is expected.

Metabolism

Omadacycline was metabolically stable following in vitro incubation with rat, dog, monkey and human liver microsomes and hepatocytes.

In intact rat (study 1000137A), unchanged omadacycline and the C4-epimer were major components in plasma, faeces and urine. In plasma, omadacycline/ C4-epimer ratio was about 0.6 following IV dosing. In bile-duct cannulated rats (study R1000163), unchanged omadacycline/C-4 epimer were the major components in bile (27.3% of dose), urine (38.4% of dose) and faeces (30.2% of dose).

Study PH-34172 is the only study addressing metabolism and excretion in monkeys, using [3H] omadacycline. Total recovery in excreta is low, partly because radioactivity is related to tritiated water. This is supported by a long t1/2 for total radioactivity in plasma, and the fact that 36.5% of total radioactivity was lost as water following freeze-drying of excreta. It is further concluded that the mass

balance data have to be interpreted with caution as residual radioactivity in the carcass was not investigated. Similar metabolic profiles were seen in monkey and rat, with few, minor metabolites in all three compartments.

Excretion

In intact rats, excretion of radioactivity following IV administration of [14C]omadacycline was complete within 48 hours, with a total recovery of 109%. Excretion was mainly via faeces (about 80%), and to a lesser extent via urine (about 30%). In bile-duct cannulated rats, excretion was via bile (24.1%), urine (29.6%) and faeces (24.5%).

In monkey, total recovery was only 73% within 336 hours following IV administration of [3H]omadacycline. Due to a substantial loss of radioactivity, the validity of the study is questioned, and the excretion data should be interpreted with caution. However, an excretion pattern similar to rat is indicated, with 36.0% of the recovered radioactivity in urine and 30.0% in faeces.

Pharmacokinetic drug interactions

Omadacycline showed very little or no inhibition for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 *in vitro*. Results from *in vitro* preincubation experiments indicated that omadacycline showed no apparent time-dependent inhibition of CYP1A2, CYP2C9, CYP2D6 or CYP3A4/5. With respect to the hepatic exposure, it can be concluded that, omadacycline is unlikely to inhibit the metabolic clearance of potential concomitant medications metabolized by CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 in humans. There are concerns about clinical relevance of no inhibition potential for CYP2B6, 2C8 and 2C19 observed *in vitro* (OC, for more details, see Clinical AR). With regards to the intestinal exposure, the Applicant is invited to justify that there is no clinical relevance on intestinal inhibition of CYP3A4 and CYP2C9 by omadacycline (OC).

Omadacycline was found not to be an *in vitro* inducer of CYP2C9, CYP2C19, CYP3A, or UGT1A1 activities or mRNA. There was a slight mRNA induction response for CYP1A1/2, CYP2B6, and CYP2C8; however, this did not translate into appreciable induction of CYP activity. In addition, omadacycline was not an *in vitro* inducer of CYP1B1 and CYP2J2 and mRNAs. It is not likely that omadacycline would act as an inducer of major drug metabolizing enzymes in humans.

Omadacycline was not substrate for OATP1B1, OATP1B3, OAT1, OAT3 and OCT *in vitro*. Omadacycline is not expected to alter the distribution or elimination of medicinal products that are substrates of human OAT1, OAT3 and OCT transporter proteins. However, for OATP1B1 and OATP1B3 new *in vitro* studies at relevant concentrations are foreseen (OC, for more details, see Clinical AR).

Moreover, the clinical study confirmed that omadacyline is P-gp substrate (For more details, see Clinical AR).

Omadacycline had no inhibition effect on the P-gp, OATP1B1, OATP1B3, OCT2, OAT3 and BCRP activity *in vitro*. Omadacycline weakly inhibited the activity of OAT1 (30% at 25 µM) *in vitro*. For OAT1B1 and 1B3 and OCT2, no *in vivo* inhibition is expected. However, it cannot be excluded that omadacycline may inhibit OAT1, OAT3 BCRP and P-gp in humans, new *in vitro* studies at relevant concentrations are foreseen (OC, for more details, see Clinical AR).

Omadacycline is not an *in vitro* inducer of P-gp and MRP2.

3.2.3. **Toxicology**

The nonclinical safety program for omadacycline was addressed in a comprehensive battery of nonclinical toxicology studies evaluating the IV and PO routes of administration. The rat and the monkey were selected as the main toxicology species and are considered relevant species. All pivotal toxicity studies were conducted in compliance with Good Laboratory Practice (GLP) regulations and according to current guidelines.

Single and repeat-dose toxicity

Single IV dose toxicity studies with IV administrations were performed in mice and rats and repeat dose toxicity studies with daily IV and PO administration were performed in rats and monkeys.

Target organs for toxicity were the hematopoietic and GI systems, adrenal glands, thymus, and liver, with low to non-existing margins of safety. In the rat, effects on the testes and spermatogenesis were also noted, while in the monkey, there was evidence of effects on the heart. Pigment discoloration (with or without iron) was noted in many tissues.

Reversible haematology findings in rats and monkeys included decreased red cell mass, haemoglobin, haematocrit, increased reticulocytes and extramedullary haematopoiesis in the spleen. The findings indicate increased erythrocyte turnover, without formation of anti-RBC antibodies. The haematology findings were noted in studies from 14 days of exposure in rats, and in the 13-week studies in monkeys.

Reversible GI related findings without safety margins were noted in all monkey studies independent of route of administration, and included emesis, diarrhoea, and faecal changes (soft/mucoid/watery). Microscopic changes including inflammatory cell infiltration in the mucosa and lamina propria, villus stunting and fusion in the small intestine, mucosal oedema, lymphoid depletion, were seen in a 14-day IV study at a high dose with exposure levels 6-7 times the clinically relevant dose. In rats, minor GI-related findings without histopathological correlates were only observed following oral administration. Similar findings are well known for other tetracyclines.

Increased adrenal gland weights were observed in both rats and monkeys that generally correlated with hypertrophy of the zona fasciculate, albeit at higher exposure levels in monkeys. Effects on thymus and spleen were observed in both rats and monkeys included reduced relative thymus weight, reduced spleen weight and lymphoid depletion in thymus and spleen. In rats, involution/atrophy of the thymus was also noted. In monkeys, microscopic findings, lymphoid depletion and hypocellularity of the bone marrow was observed together with reduced spleen weight at an exposure 7.3 times the clinically relevant exposure.

Immunotoxicity was not evaluated in an independent study, but additional immunotoxicology testing was performed in the pivotal 4-week IV monkey study. In this study lymph node/lymphoid depletion splenic lymphoid depletion and (mild) focal necrosis together with thymus gland lymphoid depletion, was observed. In the high-dose group (45 mg/kg/day, above MTD), increased total lymphocyte numbers and T cell subsets (mature T cells, helper T cells, and cytotoxic T cells) in males and a decrease in natural killer cell activity in females were seen.

Liver-related reversible findings were observed in both rats and monkeys (including increased AST, ALT and bilirubin), in general without histopathological findings. In a 37-day IV study in rats, however, clinical chemistry changes were accompanied by histopathological changes (increased liver weight, Kupffer cell activation, cellular infiltration), indicating inflammation. At exposure levels 7 times human exposure level at RHD, minimal to slight hepatocellular necrosis was observed.

Histopathological changes in cardiac tissue were observed in IV studies of 4-13 weeks duration in monkeys. The reversible findings included cardiac myofiber degeneration or myocardial vacuolar degeneration and occurred at high exposures.

Partly reversible pigmentation was identified in both rats and monkeys, with or without iron. The iron-containing pigment based on positive Perls' stain, suggesting the presence of hemosiderin, was probably a result of increased erythrocyte breakdown. The pigment deposition and discoloration of some tissues is considered a class effect seen with other tetracyclines.

Genotoxicity

Omadacycline was weakly mutagenic in L5178Y cells at concentrations at concentrations extending into the toxic range and demonstrated a weakly positive clastogenic signal in two in vitro cytogenetics assays. In the micronucleus tests in mice and rats at IV doses up to 150 mg/kg/day and 80 mg/kg/day, respectively, omadacycline is not considered genotoxic.

Carcinogenicity

No carcinogenicity studies were performed with omadacycline.

Reproductive and developmental toxicity

While no effects were observed on reproductive organs in repeat-dose toxicity studies in monkeys, testicular atrophy, oligospermia/aspermia and reduced sperm motility were observed in rats. In an IV fertility study in rats, sperm-related effects as increased weight of seminal vesicles were seen together with reduced motile sperm, sperm-count and density in the high dose group (20 mg/kg/day). At the same dose, a reduced number of corpora lutea and implantation sites, increased post-implantation loss and reduced foetal viability were observed in female rats.

In embryo-foetal toxicity studies in rats and rabbits, omadacycline-related effects on foetal development included embryo-lethality and/or increased post-implantation loss, whole body oedema, reduced foetal body weights, delayed ossification, cardiovascular and skeletal defects (rabbits only). Reduced foetal weights and mean viable foetuses were also observed in rabbits together with increased post-implantation loss.

Potential effects of omadacycline on pre- and postnatal development have been studied in rats. A slight reduction in pup weights seen at 30 mg/kg/day were not considered an adverse effect. There were no omadacycline-related effects on survival, postnatal development, behaviour or reproductive capability of F1 offspring, and the NOAEL was 30 mg/kg/day (3X the RHD AUC).

Local tolerance

Local tolerance in rabbits was good, indicating low potential for irritation.

Phototoxicity

Omadacycline is classed as "probably phototoxic" based on an in vitro 3T3 NRU phototoxicity test.

3.2.4. **Discussion on non-clinical aspects**

Pharmacology

Omadacycline inhibited the muscarinic M2 receptor with an IC_{50} value of 4.25 µM. Based on human Cmax levels (free fraction) achieved after 100 mg IV omadacycline at steady state, there is only a very limited margin of safety to inhibition of the muscarinic M2 receptor. Safety pharmacology studies have demonstrated increased heart rate in vivo and reversal of M2 agonistic effects on the SA node in vitro, indicating a potential to inhibit vagal regulation of the SA node.

IC50 values between 10 and 30 µM were found for adenosine 3 receptor, alpha 2 adrenergic 2B receptor, dopamine D3 receptor, histamine H3 receptor, muscarinic M1 receptor, opiate delta receptor, serotonin transporter, serotonin 5HT3 ion channel, pregnane X receptor (PXR).

The clinical relevance potential targets have not been addressed by the applicant. This is, however, not considered to be a safety concern due to lack of relevant findings in non-clinical studies, and low distribution across the blood-brain barrier (BBB).

At high concentrations, omadacycline resulted in statistically significant depolarisation of the membrane potential in Purkinje fibres from rabbits (at 300 µM) and dogs (at 250 µM), and in SA node from rabbit (1.5 mM). In the Langendorff preparation from guinea pigs, a slight but non-significant reduction in heart rate was observed, possibly related to a reduced slope phase 4 depolarization of the sinoatrial (SA) node. The effects on the Langendorff preparation form guinea pig was, however, minimal, not significantly different from vehicle control, and occurred at concentrations 33 times the free fraction in human plasma at intended dosing. Although other mechanisms cannot be entirely excluded, the observed depolarisation in Purkinje fibres and SA nodes occurs at test concentrations where an inhibitory effect on the Na/K-ATPase is expected (IC50 values 300-500 µM). However, due to substantial exposure margins relative to expected Cmax in patients, minor effects on heart rate and no effects on QTc in monkeys, the in vitro findings are considered to be of low clinical relevance.

Pharmacokinetics

A 10 to 20-fold difference between absorption and bioavailability was observed in rats following oral administration. It is acknowledged that different distribution properties of the active substance and metabolites could lead to erroneous estimates of total absorption relative to bioavailability. Based on total recovery of radioactivity, however, total absorption has been re-estimated to about 0.5%, slightly higher than bioavailability.

Distribution studies were conducted in males only, thus potential distribution to female reproductive organs has not been evaluated. Omadacycline is widely distributed, and distribution to female reproductive organs is expected. In addition, reproductive toxicity studies have shown effects on fertility and embryo-foetal toxicity. Taken together, the lack of distribution data in female animals is considered acceptable.

In study PH-34172 using [3H]omadacycline, total recovery in excreta is low, partly because 36.5% of total radioactivity is related to tritiated water. It is possible that tritiated water that was formed in vivo may have been lost during respiration (expired air was not collected) and via ambient evaporation from urine and faeces prior to having been collected from the metabolism cages. Additional tritiated water likely remained in the animals, distributed in body water, beyond the final collection interval (336 hours), which represents slightly less than 3 half-lives of tritiated water (93.2 hours). However, there is little concern of sustained retention of drug-related material in the body, based on the full recovery observed in rats (~ 80% and ~ 30% recovery in faeces and urine, respectively after IV administration of [14C]-omadacycline; Study R1000137A) and, more importantly, the 95.5% recovery of 14C-radioactivity in humans (Study CPTK796A2101).

Repeat-dose toxicology

In some organs the pigment deposition correlated with cellular damage e.g., 14-week study in monkeys with canicular bile stasis. Pigment deposition was dose-related and persistent after discontinuation of treatment in most of the organs. The Applicant clarified that this statement was made on the basis of staining for the presence of bile and not on any histological evidence of bile stasis. Moreover, it was demonstrated that no histologic changes were noted to the bile duct or the bile ductules within the liver that would indicate bile stasis. The Fouchet's stain on the liver samples confirmed the accumulation of intracanalicular bile. Canalicular bile stasis is seen as a primary form of drug toxicity but can also be seen as a secondary event in a variety of pathologic processes, including gram negative septicemia (Arias et. al., 1994). The latter was considered as particularly prominent possibility in the present study, given the histologic alterations in the intestine.

Severe cardiac myofiber degeneration or myocardial vacuolar degeneration has been observed in 4-week and 13-week studies in monkeys with the lowest 3.8 multiple of systemic exposures (AUC) as in therapeutic use. As no adequate risk mitigation measures can be proposed, this should be reflected in

the SmPC to complement toxicology profile of the drug. The SmPC has been updated with additional data in preclinical section 5.3 on cardiac myofiber degeneration and myocardial vacuolar degeneration observed in studies with monkeys. However, text should be further revised to include exact safety margins, method of administration and duration of the other study as current information is too vague.

In general, dose-related exposure levels have been observed in monkeys at IV doses up to 40 mg/kg/day. In study report no. 1116-007, however, a 17-fold increase in AUC, and a 46-fold increase in Cmax was observed between 5 and 45 mg/kg at study day 1. Considering the atypical TK parameters in this study, leading to moribundity and deaths at 45 mg/kg/day, dosing errors cannot be excluded.

Genotoxicity and carcinogenicity

The lack of carcinogenicity studies is considered acceptable, due to lack of genotoxic potential, and the intended short-term treatment (up to 14 days).

Phototoxicity

Phototoxicity is known as a class effect of tetracyclines, and omadacycline is classified as "probably phototoxic". However, the skin was in the group of tissues showing the lowest exposure 2 hours after omadacycline administration, and very low residual radioactivity within 24 hours after administration. Omadacycline was not considered to have a significant phototoxicity risk in humans and no photosensitivity was reported in omadacycline treated subjects. Therefore, no specific warning for phototoxicity is warranted in the SmPC.

3.2.5. **Conclusion on non-clinical aspects**

Nuzyra may be granted a marketing authorisation from a non-clinical point of view.

3.3. Clinical aspects

3.3.1. **Pharmacokinetics**

Across 22 clinical biopharmaceutic and clinical pharmacology studies, 695 subjects were exposed to omadacycline. The maximal doses of omadacycline investigated were: 600-mg as a single iv and oral dose; 200-mg once given daily for 7 consecutive days as a multiple iv dose regimen; and 600-mg every 24 hours (q24h) for 5 consecutive days as multiple oral dosing regimen.

A population PK model for omadacycline was developed using data from 14 Phase 1 studies, two Phase 3 studies conducted in patients with ABSSSI (Studies PTK0796-CSSI-0804 and PTK0796-ABSI-1108) and one Phase 3 study conducted in patients with CABP (Study PTK0796-CABP-1200).

Bioanalysis:

During the development, omadacycline concentrations were assayed in several biological media, plasma, urine, dialysate, bronchiolar lavage fluid and cellular pellets. In addition, tigecycline, urea and verapamil were analysed. The performance of the bioanalytical methods was demonstrated by validation performed in compliance with principles of GLP and in accordance with requirements of the FDA Bioanalytical Method Validation Guidance for Industry and Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev1).

For all the clinical studies, inter-day accuracy and precision data demonstrated the reliability of the assays. Samples were stored at -70°C, and the analytes were shown to be stable under these

conditions in the validation studies. Incurred sample reanalysis (ISR) was not performed for omadacycline in several of the early studies. It was also not performed in some instances where only a small number of samples were analysed (in accordance with the sample analysis plan). For the remaining studies, at least 2.5%-10% of the samples were re-assayed as ISR and at least 67% of the results were within 20% of the original assay result. Overall, all bioanalytical methods used were robust and reliable.

Absorption:

Following an oral dose of 300 mg the absolute bioavailability is around 34%; a value that probably is representative of the fraction absorbed from the gastrointestinal tract (based on a low non-renal clearance). Thus, the oral omadacycline drug product can be tentatively classified as a BCS 3 product, with overall absorption likely limited by low permeability, not dissolution or solubility.

Food has a large negative effect on the systemic exposure of oral omadacycline, especially when food is consumed close in time compared to the oral dosing. A high fat meal has a larger negative impact on the systemic exposure than a low fat meal, and the presence of divalent cations in the food (e.g., dairy products) seems to reduce the exposure further.

Table 1. Summary of food effect results.

Study No.	Objective: Primary or Secondary	Oral Dose of omadacycline, mg	Number of M/F subjects	Formulation	Time of food intake relative to time of oral dose administration (+/-) h	Type of food	% change, either as the arithmetic or geomean in AUC_∞ from fasting condition
PTK0796-OBAV-0502	Secondary	200	8M	Amorphous Free base capsules	- 0.5	High fat meal	-80.6
		400	8M		- 1.5	Low fat meal	-19.7
PTK0796-BEQV-0806	Secondary	200	6M	Tosylate salt (Form 1) in Qualcaps	+ 1	Low fat meal	-33.6
		200	6M	Tosylate salt (Form 1) in Capsugel	+ 1	Low fat meal	-58.9
PTK0796-BAVA-0810*	Secondary	300	7M/1F (fasted) 5M/3F (fed)	Tosylate salt (Form 1) tablet	+ 2	Low fat meal	-8.2
PTK0796-BEQW-0809	Primary	300	8M/8F	Tosylate salt (Form 1) in a capsule	-2	High fat meal (Dinner)	Males: -38.8 Females: -54.2
					+ 1	Low fat meal (Breakfast)	Males: -19.5 Females: -32.3
CPTK796A2103	Primary	300	38M/2F	Tosylate salt (Form 3) tablet	+1	Light, non-fat meal	-26.3
					+2	Light, non-fat meal	-9.4
					+ 2	Standard, low-fat meal	-11.1
					+2	High fat meal	-12.8
PTK0796- FDEF-15101	Primary	300	15M/17F	Tosylate salt (Form 3) tablet	-4	Standard high-fat (nondairy) meal	-13.4
					-2	Standard high-fat (nondairy) meal	-40.9
					-2	Standard high-fat meal including dairy	-60.3
PTK0796- DDI-17106 (Periods 1 vs, 3)	Primary	300		Tosylate salt (Form 3) tablet	-1.5	Light meal consisting of toast and orange juice (nondairy)	-24.7

* Parallel study design
AUC_∞ = area under the (concentration-time) curve from time 0 to infinity, F = female, M = male.

In the proposed SmPC it is stated: "The film-coated tablets are to be taken after fasting for 4 hours and can be taken with water. After taking the tablet, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours…"

The possible negative impact of divalent cations on the exposure of omadacycline when taken post-dose has not been studied.

It has not been studied in a dedicated PK study whether the different loading dose options (oral or iv) lead to similar AUCs. The AUCs achieved by different maintenance dose options, 100 mg IV infusion QD or an oral 300 mg dose QD, were compared in a cross-over study in healthy subjects.

Table 2. Geometric mean ratio and 90% confidence intervals for PK parameters

Parameter (Unit)	T2/T1 (300 mg FMI 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)

Distribution:

Across several studies employing iv omadacycline (50-, 100- or 200-mg), the volume of distribution estimates were approximately 200-300 L, with preferential compartmentalisation to plasma. Omadacycline is weakly bound (~20 %) to human plasma proteins in the concentration range of 10-10000 ng/mL.

Study PTK0796-BAL-15104 was an open-label, parallel group, multiple IV dose study to assess intra-pulmonary steady-state concentrations in epithelial lining fluid (ELF) and alveolar cells (AC), and pulmonary distribution time-course, of omadacycline and tigecycline in healthy adult subjects with the aid of bronchoscopy.

Table 3. Summary of the AUCAC, AUCELF, and AUCPlasma, Ratio of AUCAC/AUCplasma, and Ratio of AUCELF/AUCplasma by Treatment

Descriptive Statistics	Omadacycline		Tigecycline	
	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.

Elimination:

The systemic clearance of omadacycline in healthy subjects is approximately 11 L/h and half-life of omadacycline of 17- 24 hours was observed in clinical studies.

Study CPTK796A2101 was an open-label study to assess the absorption, distribution, metabolism, and elimination of [14C]-labelled PTK796, and the safety and tolerability of PTK796 and metabolites, in 6 healthy male subjects following a single oral dose of 300 mg PTK796.

Table 4. Excretion of total radioactivity (% of dose) in humans following an oral dose of 300 mg [14C]PTK796

	Subject							
	5101	5102	5103	5104	5105	5106	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: PT-Table 14.2-2.4 and PT-Table 14.2-2.5

No metabolites were detected. Several impurities and degradation products were characterized in both the dosing solution and biological samples (plasma, urine and faeces). In all bio fluids, the C-4 epimer of PTK796 (known to form upon standing) was observed. PTK796 in plasma reached Cmax between 1 and 4 h.

Renal excretion of omadacycline was evaluated in four clinical pharmacology studies:

Table 5. Summary of Mean Percent of Dose Excreted in the Urine and Renal Clearance of Omadacycline Across Studies

Study No	Dose	Route of Drug Administration	Formulation	N (M/F)	Mean	
					Fe, %	CL_r, L/h
CPTK796-A2101	300-mg	Oral	^{14}C-labeled omadacycline-tosylate salt Form 1	6M	14.4	ND
PTK0796-RENL-15102 (healthy subjects)[a]	100-mg	iv	Lyophilisate vials (tosylate salt)	6M/2F	27.0	3.06
PTK0796-UUTI-15103[b]	200-mg iv (Day 1); 300-mg po q24h (Days 2-5)	iv/Oral	iv: Lyophilisate vials (tosylate salt) (Day 1); po: Crystalline tosylate salt (Form 3) tablets (Days 2-5)	11F	10.76	2.42
	300-mg q12h (Day 1); 300-mg po q24h (Days 2-5)	Oral	Crystalline tosylate salt (Form 3) tablets	10F	12.74	2.71
	450-mg q12h (Day 1); 450-mg po q24h (Days 2-5)	Oral	Crystalline tosylate salt (Form 3) tablets	10F	12.19	2.80
PTK0796-MDPO-16105[b]	300-mg q24h for 5 days	Oral	Crystalline tosylate salt (Form 3) tablets	21M/5F	8.71	3.28
	450-mg q24h for 5 days	Oral			6.85	2.38
	600-mg q24h for 5 days	Oral			8.64	3.05

CL_r = renal clearance, F = female, F_e = percent of dose excreted in the urine, iv = intravenous, M = male, ND = not determined, po = per oral, q12h = every 12 hours, q24h = every 24 hours, CL_r = renal clearance, F = female, F_e = percent of dose excreted in the urine, iv = intravenous, M = male, ND = not determined, po = per oral, q12h = every 12 hours, q24h = every 24 hours.

[a]The data presented are from the healthy subject cohort of the study.

[b]Multi-dose study; the Fe and CL_r values are from the final (oral) dose.

No discernible omadacycline metabolism was observed in studies of human liver microsomes, hepatocytes, liver sub-cellular fractions, or recombinant preparations of human drug metabolizing enzymes.

Dose proportionality for the oral formulation was addressed via the following studies:

Table 6. Summary of Mean Oral Pharmacokinetic Parameters of the Tosylate Salt Polymorphic Form 3 of Omadacycline Across Studies in Healthy Subjects

Study	Dose, mg	N (M:F)	Mean Values C_{max}, ng/mL	t_{max}[a], h	AUC[b], ng·hr/mL	$t_{1/2}$, h
Multiple Dose						
PTK0796-UUTI-15103 (Group 1, 2 and 3, Day 5)[c]	200-mg iv on Day 1 followed by 300-mg q24h days 2-5	11F	1117.20	3.0	13156	NDd
	300-mg po q12h on Day1 followed by 300-mg q24h X days 2-5-	10F	1116.00	3.0	13500	ND
	450-mg po q12h on Day1 followed by 450-mg q24h X days 2-5	10F	1487.10	3.0	19829	ND
PTK0796-MDPO 16105	300-mg q24h X 5 days	21M; 5F	809	2.5	9267	15.5
	450 mg q24h X 5 days		1077	2.5	13367	16.8
	600 mg q24h X 5 days		1306	2.5	16420	16.8

AUC = area under the concentration time curve, 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, C_{max} = maximum plasma concentration, CV = coefficient of variation, F = female, iv = intravenous, M = male, ND = not determined, q12h = every 12 hours, q24h = every 24 hours, $t_{1/2}$ = terminal half-life, t_{max} = the time the maximum plasma concentration was observed.

[a] Median.

[b] AUC single dose = AUC_{∞};, AUC multiple dose = AUC_{0-24h}

[c] Day 5 data.

[d] Not determined.

A summary of PK parameters following single iv doses of omadacycline ranging from 25- to 600-mg is summarized below:

Table 7. 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: CSR PTK 0796-SDES-0501 Table 11-1.

Omadacycline exhibits proportional PK over the entire dose range (25 to 600 mg) as assessed by area under the concentration time curve (AUC).

Potential time-dependency in PK and estimates of intra and inter individual variability was not presented.

The multiple dose IV and oral administration with once a day dose setting resulted in similar accumulation levels of omadacycline with accumulation ratio of 1.5 pointing on week accumulation of the substance.

Special populations:

Impaired renal impairment was studied in study PTK0796-RENL-15102 which was an open-label, single-dose, two period, parallel group study. ESRD subjects on stable hemodialysis (n=8) received single dose omadacycline 100-mg via a 30-min iv infusion followed by an additional iv infused dose of omadacycline after a washout period of 10 to 20 days, and matched healthy subjects (n=8) received single dose omadacycline 100-mg iv via a 30-min infusion.

Table 8. Statistical Comparison of Pharmacokinetic Parameters Between ESRD Subjects on Stable Hemodialysis and Matched Healthy Control Subjects (PTK0796-RENL-15102)

PK parameter	Cohort	Geometric Mean	Ratio of Geometric Mean (%)	90% Confidence Interval
AUC_{last} (ng·h/mL)	Cohort 1 Period 1 (Test)	9210	103	85.8 - 124.3
	Cohort 2 (Reference)	8910		
AUC_{∞} (ng·h/mL)	Cohort 1 Period 1 (Test)	10100	105	87.7 - 125.8
	Cohort 2 (Reference)	9610		
C_{max} (ng/mL)	Cohort 1 Period 1 (Test)	1780	94.3	72.4 - 122.7
	Cohort 2 (Reference)	1880		

Cohort 1 Period 1 (Test): ESRD subjects on stable hemodialysis (dosing after dialysis).
Cohort 2 (Reference): Healthy subjects.
Source: PTK0796-RENL-15102 CSR Table 11-6.

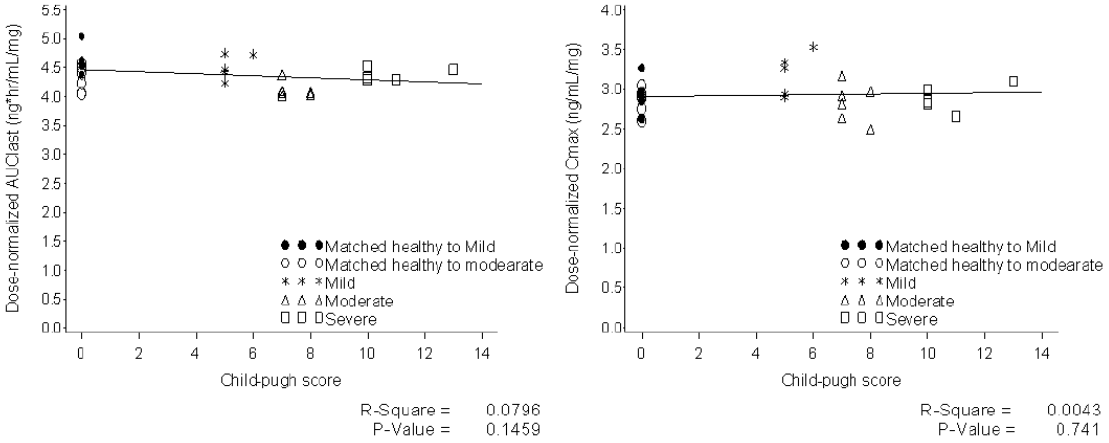
Table 9. Statistical Comparison of Pharmacokinetic Parameters Between ESRD Subjects on Stable Hemodialysis for Period 2 (Test) and Period 1 (Reference) (PTK0796-RENL-15102)

PK parameter	Cohort	Geometric Mean	Ratio of Geometric Mean (%)	90% Confidence Interval
AUC_{last} (ng·h/mL)	Period 2 (Test)	9090	98.8	94.8 - 102.9
	Period 1 (Reference)	9210		
AUC_{∞} (ng·h/mL)	Period 2 (Test)	10000	99.5	96.1 – 103
	Period 1 (Reference)	10100		
C_{max} (ng/mL)	Period 2 (Test)	2180	123	98.3 - 153.6
	Period 1 (Reference)	1780		

Cohort 1 Period 1: Omadacycline 100 mg ESRD subjects on stable hemodialysis (dosing after dialysis); Cohort 1 Period 2: Omadacycline 100 mg ESRD subjects on stable hemodialysis (dosing before dialysis).
Source: PTK0796-RENL-15102 CSR Table 11-7.

18 hepatically impaired subjects and 12 healthy subjects were studied in study CPTK796A2201, an open-label, fixed-sequence study. During period 1, subjects with mild hepatic impairment (Group 1) received a single 100-mg iv dose of omadacycline, and subjects with moderate and severe hepatic impairment (Groups 2 and 3, respectively) received a single 50-mg iv dose of omadacycline. During period 2, after 7 days' washout, Groups 1 and 2 received a single oral dose of 300-mg or 150-mg of omadacycline, respectively, after a 10-hour fast; fasting continued until 4 hours after dose administration.

Table 10. Dose-Normalized AUClast and Cmax of PTK796 vs. Child-Turcotte-Pugh score, IV infusion. Healthy Subjects Were Assigned a Score of Zero



Note:Solid line represents regression line.
Log transformed AUClast and Cmax values are plotted.

Table 11. Geometric Mean Ratio Comparison of and 90% Confidence Intervals for Dose normalized Primary PK Parameters (Hepatic Impaired Subjects/Healthy Subjects) (CPTK796A2201)

	Group 1[1]		Group 2[2]		Group 3[3]
Parameter	**100-mg iv Omadacycline**	**300-mg oral Omadacycline**	**50-mg iv Omadacycline**	**150-mg oral Omadacycline**	**50-mg iv Omadacycline**
AUC_{last} (ng·h/mL)	0.90 (0.73, 1.11)	0.79 (0.5, 1.24)	0.85 (0.75, 0.97)	1.02 (0.75, 1.4)	1.08 (0.91, 1.27)
AUC_{∞} (ng·h/mL)	0.86 (0.69, 1.07)	0.79 (0.5, 1.24)	0.88 (0.78, 0.99)	1.02 (0.75, 1.4)	1.08 (0.91, 1.27)
C_{max} (ng/mL)	1.42 (1.1, 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: CPTK796A2201 CSR Table 11.

Race was not found to be a significant covariate in the popPk analysis. With only 15 Asians in the datasets, even with an improved popPK model, it is difficult to draw conclusions on the similarity of PK in Asians compared to other groups.

Race	Caucasian	474 (77.3)
	Black	109 (17.8)
	Asian	15 (2.4)
	Other	15 (2.4)

Body Weight was not included in the final popPk model, despite being expected to affect omadacycline PK. Sex was included as a covariate on clearances and volumes, but may be highly correlated to weight and it would be appropriate to update the popPk model to include body weight instead (see popPK section and list of questions).

Age was not found to be a significant covariate in the popPK analysis. Since exposure is not changed in renal impairment, CrCl or age were not expected to be significant covariates.

Interactions:

Study PTK0796-DDI-17106 was a three-period, open-label, single-sequence study to evaluate the effect of verapamil ER on the PK of a single oral dose of 300 mg omadacycline in healthy adult

subjects. The verapamil vs control geometric mean ratio of AUC∞ and Cmax were 124.58% and 113.55%, respectively (90% CI [108.457, 143.118], and [101.249, 127.361]).

popPK model

The applicant has developed a popPK model for Omadacycline in several steps described in reports ICPD 00397-1 and ICPD 00397-2.

Data

Data from ten Phase 1 studies (Studies PTK 0796-OBAV-0502, TK 0796-BEQU-0801, PTK 0796-BEQV-0806 , PTK 0796-BAVA- 0810 , PTK 0796-MDOR-0901 , CPTK796A2103 , CPTK796A2201, CPTK796A2104 , CPTK796A2101, and PTK0796-FDEF-15101) were utilized to develop the original omadacycline population PK model. Data from these studies were pooled with data from three additional Phase 1 studies (Studies PTK0796-RENL- 15102 , PTK0796-BAL-15104 and PTK0796-MDPO-16105), a Phase 1b uncomplicated urinary tract infection (uUTI) patients (Study PTK0796-UUTI-15103), two Phase 3 studies conducted in patients with skin infections (Studies PTK0 796-CSSI-0804 and PTK0796-ABSI-1108 and one Phase 3 study conducted in patients with CABP (Study PTK0796-CABP-1200)**.** The final model was further evaluated by using data from Study PTK0796-ABSI-16301, a dataset which was not utilized during model development. PK samples with omadacycline concentrations below the LLOQ were excluded from the population PK analysis.

Table 12. Summary of the number of subjects and plasma omadacycline concentrations available and included in the PK analysis

Study	Total number of PK samples	Number of samples below the LLOQ excluded	Number of suspected outlier excluded	Number of samples included in analysis[a]	Number of subjects included in analysis
PTK0796-OBAV-0502	921	122	6[b]	793	63
PTK0796-BEQU-0801	588	117	0	471	32
PTK0796-BEQV-0806	352	49	1[b]	302	30
PTK0796-BAVA-0810	678	27	14[b]	637	40
PTK0796-MDOR-0901	622	3	1[b]	618	24
PTK0796A2103	2182	13	2[b]	2167	40
PTK0796A2104	504	1	0	503	22
PTK0796A2201	689	116	1[b]	572	30
PTK796A2101	96	22	0	74	6
PTK0796-FDEF-15101	1488	66	0	1422	32
Total used for developing the original population PK model	**8120**	**536**	**25**	**7559**	**319**
PTK0796-RENL-15102[c]	160	5	1	154	16
PTK0796-BAL-15104	451	3	2	446	41
PTK0796-MDPO-16105	1870	17	0	1853	26
PTK0796-UUTI-15103	640	1	1	638	31
PTK0796-CSSI-0804[d]	243	4	5[e]	234	50
PTK0796-ABSI-1108	292	7	12	273	80
PTK0796-CABP-1200	187	0	13	174	50
Total used for refining population PK model	**11963**	**573**	**59**	**11331**	**613**
PTK0796-ABSI-16301	761	14	0	747	202
Total used for external validation	**761**	**14**	**0**	**747**	**202**

Note: Abbreviations are provided in the Abbreviation Listing.

a. Outliers, data below the LLOQ and placeholders for missing samples were retained in the analysis dataset, but were flagged for exclusion using OMIT variable within NONMEM.

b. Determined to be outlier in original PPK analysis and retained as outlier for this analysis.

c. Data from treatment period where subjects receive omadacycline before dialysis (Treatment Period 2) were omitted from the analysis.

d. 7 subjects removed from dataset as oral omadacycline doses were not administered under fasted conditions.

e. 1 outlier removed as observation resulted in error in model minimization process.

Table 13. 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	474 (77.3)	—	—	—	—
	Black	109 (17.8)	—	—	—	—
	Asian	15 (2.4)	—	—	—	—
	Other	15 (2.4)	—	—	—	—
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)	—	—	—	—

Note: Abbreviations are provided in the full report Abbreviation Listing in original report.

Final model

The final population PK model for omadacycline was a linear, three-compartment model with zero order IV input and 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 modelled as a subcompartment of Vp1. Sex was estimated as a covariate for CL, CLd1, VP1 and Vp2.

Sex and body weight are likely to be correlated. Many covariates that are correlated were tested. It would have been useful if the applicant had plotted the covariates against each other and provided the R2 value prior to the covariate analysis to limit covariates to be tested (i.e. chose one of body weight or BSA instead of testing sex, body weight, BSA, BMI and height).

Overall, the final popPK analysis shows model misspecification. The pc-VPC for plasma concentration show the simulated 50th percentile is lower than the observed data. The simulated lower percentile is also lower than observed while the upper percentile looks adequate (figure 19). The pc-VPC for ELF show model misspecification and the lower and upper percentiles of the observed data are not included (figure 20). The external validation VPCs also indicates model misspecification (figure 21 and 22). These issues need to be solved for the probability of target attainment simulations to be trustworthy.

Table 14. 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 Capsugels 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.

Figure 19. Prediction-corrected comparison of observed and simulated omadacycline plasma concentrations

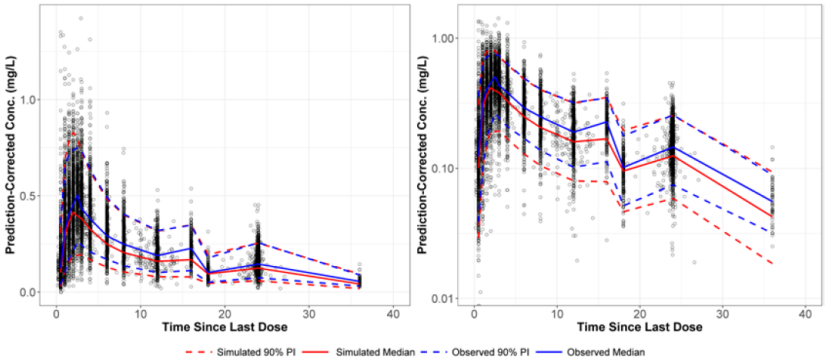


Figure 20. pc-VPC for ELF data

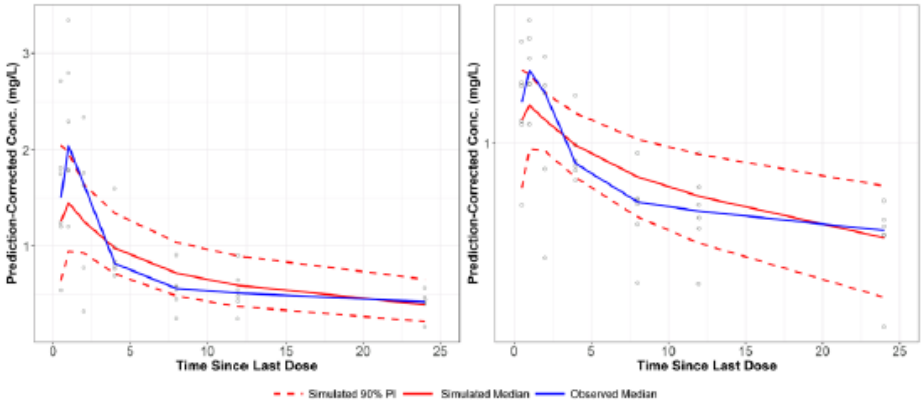
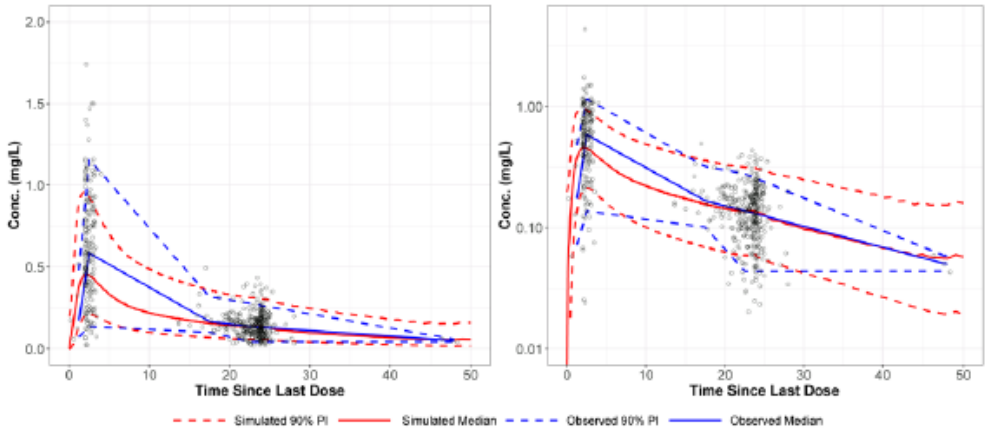
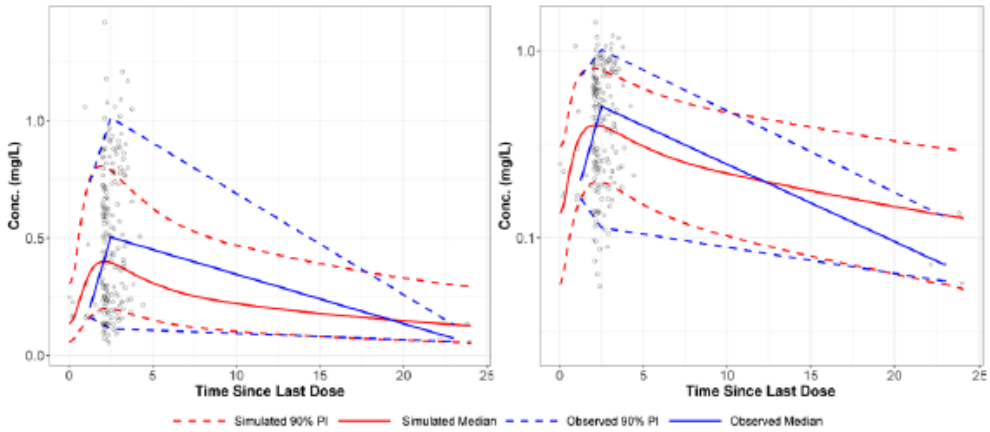


Figure 21. Visual predictive check using data following administration of omadacycline 450 mg in Study PTK0796-ABSI-16301



Note: One of 4.33 mg/L at 2.25 h post-dose is not displayed.
Abbreviations are provided in the Abbreviation Listing.

Figure 22. Visual predictive check using data following administration of omadacycline 300 mg in Study PTK0796-ABSI-16301



3.3.2. **Pharmacodynamics**

3.3.2.1. Mechanism of action

The available genetic, biochemical and structural data support that omadacycline is similar in structure to minocycline and binds to the primary tetracycline binding site of the 30S ribosomal subunit to inhibit bacterial protein synthesis.

3.3.2.2. Bactericidal vs bacteriostatic activity of omadacycline

Minimal bactericidal concentration and time-kill data suggest that omadacycline is bacteriostatic against *Enterococcus faecalis*, *Enterococcus faecium*, *S. aureus* and *Escherichia coli*, but displays slow bactericidal activity against *M. catarrhalis* and rapid bactericidal activity against *Haemophilus influenzae* and *S. pneumoniae*. This spectrum of activity is in line with the tetracycline class, which is generally considered bacteriostatic rather than bactericidal.

3.3.2.3. Post-antibiotic effect

There are sparse, variable *in vitro* and *in vivo* data suggesting a possible post-antibiotic effect of 2-3 hours in *S. aureus* and *S. pneumoniae*.

3.3.2.4. Intracellular activity against Legionella pneumophila

An *in vitro* study demonstrated activity of omadacycline against intracellular *L. pneumophila* and *S. aureus* at minimal inhibitory extracellular concentration (MIEC) to MIC ratio of ≤¼.

3.3.2.5. Activity in the presence of body fluids or additives

Omadacycline MIC for *S. aureus*, *S. pneumoniae*, *E. coli* and *H. influenza* is not affected *in vitro* by the presence of human serum or bovine surfactant but appears to be negatively affected for selected organisms (*E. coli*, *K. pneumoniae*, *S. saprophyticus*, *S. aureus*) in the presence of human urine (8-fold higher) or high magnesium ion concentrations (16-fold higher). The mechanism for this effect is not clear but may be an important factor in the food effect (notably milk and cation-containing antacids and multivitamins) on bioavailability (see section 3.3.1. Pharmacokinetics).

3.3.2.6. Resistance

In vitro testing of global Gram positive and negative SENTRY surveillance isolates (the majority from 2016) expressing one or more *tet* genes indicates that omadacycline may be able to withstand many of the classical tetracycline-specific resistance mechanisms of both efflux (tet(A),(B),(C),(D),(G),(J),(K),(L)) and ribosomal protection (tet(M),(O),(W)). This is supported by a number of smaller *in vitro* studies of tetracycline-resistant organisms. However, like other tetracyclines, omadacycline is inactivated via hydrolysation by tetracycline monooxygenase *tet*(X).

One of the mechanisms of tigecycline resistance is alteration in the conserved KYKD motif of RpsJ, a ribosomal structure protein. In an *in vitro* study (CICbioGUNE_2018 milestone), the mode of omadacycline binding to the KYKD motif was shown to be different than that of tigecycline. Additionally, during SENTRY surveillance studies 2009-216, the incidence of these mutations was rare. It is considered unlikely that these mutations will develop and spread rapidly during clinical use.

Omadacycline activity may be reduced in the presence and/or up-regulation of non-specific efflux pumps, such as the RamA-controlled RND-type efflux pump AcrAB, commonly found in Gram negative species, and MexXY, expressed by *P. aeruginosa*. However, the tetracycline class antibiotics have not been reported to be a prominent substrate of the AbcA efflux system.

Gly180Val mutation leads to an increase in mexC expression which probably has an impact on the expression level of MexCD efflux pump. These mutations are considered to be specific for *P. aeruginosa* but could lead to omadacycline resistance development in other organisms as a result of nfxB-homolog alteration. Nonetheless, OMC is not intended for infection caused by *P. aeruginosa* and other organisms possessing this mutation are not known or their frequency is rare so far. Thus, this is considered as a hypothetical risk.

3.3.2.7. Cross resistance

The in vitro activity of omadacycline was not affected in *in vitro* studies against *S. aureus, H. influenzae,* and *S. pneumoniae* strains with macrolide-, ciprofloxacin- or erythromycin-resistance, and *E. coli* expressing beta-lactamases.

Clinical isolates displaying resistance to other antibiotics were selected from the 2016 SENTRY surveillance collection. The correlation (presented as R^2 values) between MIC for omadacycline and other antibiotics was low for most antibiotics (highest R^2 of 0.5865 vs tigecycline, for *E. coli* and *K. pneumoniae* isolates).

3.3.2.8. Laboratory selection of resistance

Single-step (4x, 8x and 16x MIC of omadacycline) and serial passage (10 days' sub-MIC) selection of resistance was investigated in four strains of *S. aureus* with (3) and without (1) pre-existing *tet*(K), (L) or (M) resistance genes. The resistance frequency was determined to be $<1.5x10^{-8}$.

In another study, $\leq 2.9 \times 10^{-9}$ CFU/mL inocula of 5 *H. influenzae* strains failed to produce a drug-resistant (5x MIC) sub-population when exposed to 3x or 5x MIC over 48 hours in the one-compartment model.

3.3.2.9. Pharmacodynamic interactions with other medicinal products

Overall, no consistent trends of antagonism or synergy with other antibiotics classes were observed according to fractional inhibitory concentrations (FIC) (checkerboard analysis) using CLSI broth micro-dilution methodology for *E. coli*, *S. aureus*, *Enterococcus spp*., and *S. pneumoniae* strains.

3.3.2.10. In vitro spectrum of activity

The *in vitro* activity of omadacycline was tested against over 100,000 bacterial isolates, collected by global SENTRY surveillance programs (of which approximately one third came from Europe and one half from North America) between 2009 and 2016.

Table 15. Multi-year Global Surveillance Omadacycline Distribution, Gram(+)Isolates

Species[a]	Total	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Staphylococcus aureus (all)	29280	0.12	0.25
Staphylococcus aureus (methicillin-susceptible)	17339	0.12	0.25
Staphylococcus aureus (methicillin-resistant)	11941	0.12	0.5
Staphylococcus aureus (tetracycline-resistant)	2474	0.12	0.5
Coagulase-negative staphylococci (all)[b]	4928	0.25	1
Coagulase-negative staphylococci (methicillin-susceptible)	1415	0.12	0.5
Coagulase-negative staphylococci (methicillin-resistant)	3513	0.25	1
Enterococcus faecalis (all)	5711	0.12	0.5
Enterococcus faecalis (vancomycin susceptible)	5548	0.12	0.5
Enterococcus faecalis (vancomycin resistant)	163	0.12	0.5
Enterococcus faecium (all)	3195	0.06	0.25
Enterococcus faecium (vancomycin susceptible)	1593	0.06	0.25
Enterococcus faecium (vancomycin resistant)	1602	0.06	0.25
Streptococcus pneumoniae (all)	9980	0.06	0.12
Streptococcus pneumoniae (penicillin susceptible)	6089	0.06	0.12
Streptococcus pneumoniae (penicillin resistant)	1030	0.06	0.12
Streptococcus pneumoniae multidrug resistant (MDRSP)	3078	0.06	0.12
Streptococcus pneumoniae (tetracycline-resistant)	2873	0.06	0.12
Streptococcus agalactiae (all)	2554	0.06	0.12
Streptococcus agalactiae (macrolide resistant)	1009	0.12	0.12
Streptococcus pyogenes (all)	2561	0.06	0.06
Streptococcus pyogenes (macrolide resistant)	332	0.06	0.12
Streptococcus spp. viridans group (all)[c]	1387	0.06	0.12
Streptococcus spp. viridans group (penicillin susceptible)	1597	0.06	0.12
Streptococcus spp. viridans group (penicillin resistant)	104	0.06	0.12
Streptococcus anginosus group (all)[d]	465	0.06	0.12

Species[a]	Total	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)

EUCAST = European Committee on Antimicrobial Susceptibility Testing, 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]EUCAST breakpoints applied for species groupings.

Source: 2.7.2.4. adapted from applicant's Summary of Clinical Pharmacology Studies – Special Studies- Micro

Table 16. Multi-year Global Surveillance Omadacycline Distribution, Gram(-) Isolates

Species	Total	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Enterobacteriaceae (all)	32563	2	>4
Enterobacteriaceae (ESBL-phenotype)	5601	2	>4
Escherichia coli (all)	14091	1	2
Escherichia coli (ESBL-phenotype)	2953	1	4
Klebsiella pneumoniae (all)	6792	2	>4
Klebsiella pneumoniae (ESBL-phenotype)	2214	2	>4
Enterobacter cloacae	2703	2	>4
Haemophilus influenzae	4683	1	2
Moraxella catarrhalis[a]	408	0.25	0.25
Acinetobacter baumannii	2754	2	8
Stenotrophomonas maltophilia	1023	2	8
Pseudomonas	1986	32	>32

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.

Source: 2.7.2.4. adapted from applicant's Summary of Clinical Pharmacology Studies – Special Studies – Micro

Omadacycline has variable activity against *Acinetobacter* spp., and *Stenotrophomonas* spp. (≤8 µg/mL), and is not active against *Proteus* spp., *Providencia* spp., *Morganella* spp., and *P. aeruginosa*.

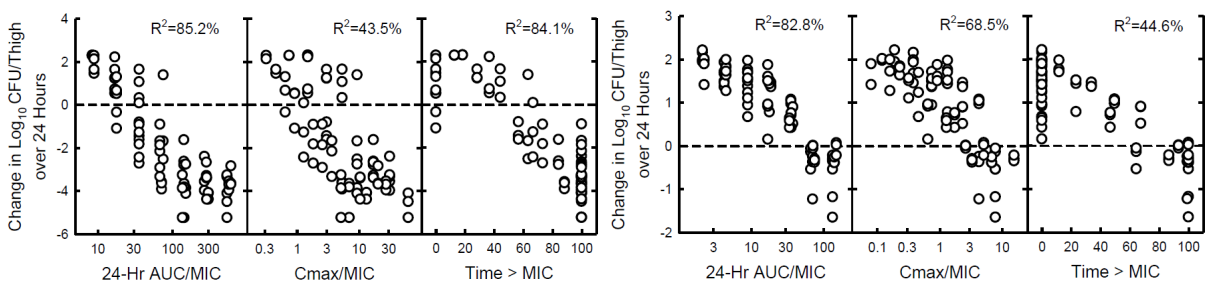
3.3.2.11. Non-clinical PK/PD

Neutropenic mouse thigh model

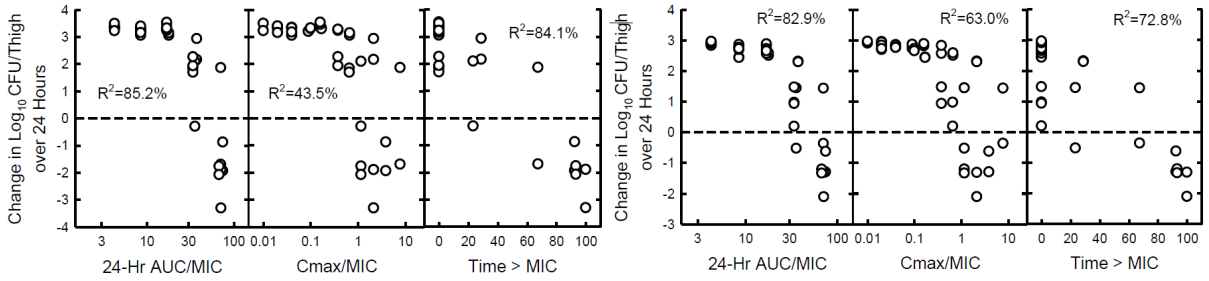
In an initial study (Craig 2006), neutropenic mice (2-3 test animals per dose) injected with test strains were administered fractionated SC omadacycline doses ranging from 0.156 to 40 mg/kg using dosing intervals of 3, 6, 12 or 24 hours. Similar dose-response relationships were observed with 3-, 6-, and 12-hourly intervals. The 24-hr regimen was least effective. AUC_{0-24}:MIC had the highest R^2 and least variability, particularly at high and low extremes, than Cmax/MIC or Time>MIC, identifying AUC:MIC as the index best correlated to efficacy (this is true for other tetracyclines):

Figure 1. Relationship for different PK/PD indices in *S. pneumoniae* (A), *S. aureus* (B) and *E. coli* (C) in the neutropenic mouse thigh model (Craig 2006)

A. *Streptococcus pneumoniae* B. *Staphylococcus aureus*



B. *Escherichia coli* (2)



Source: submitted report Craig 2006 Figures 8-10.

Following this, 12-hourly dosing regimens were tested against strains with varying omadacycline MIC (3 MSSA, 2 CA-MRSA, 12 *S. pneumoniae*, 3 *E. coli* and 1 *K. pneumoniae*). Across strains, the dose required for bacterial stasis varied over 200-fold (from 0.368 to 74.4 mg/kg/12h), and the AUC:MIC for stasis varied 5.5-fold (14.9 to 81.8), with the lowest values obtained for *S. pneumoniae* and *E. coli* strains and the highest for some *S. aureus* strains and for *K. pneumoniae*.

In a second study, Andes *et al.* reported R^2 of 0.92, 0.87 and 0.88 for AUC:MIC for *S. aureus*, *S. pneumoniae* and *E. coli*, respectively, however no comparison to other potential PK/PD indices were presented for comparison.

Table 17. PD targets in the neutropenic murine thigh model, (Craig and Andes studies)

	Craig 2006			Andes Thigh 2017				
Organism	**MIC (µg/mL)**	**Static Dose (mg/kg/12h)**	**Stasis Plasma 24-Hr AUC/MIC**	**MIC (µg/mL)**	**Static Dose (mg/kg/12h)[a]**	**Stasis Plasma 24-Hr AUC/MIC**	**1 log kill dose (mg/kg/12h)[a]**	**1 log kill Plasma 24-Hr AUC/MIC**
S. aureus ATCC 29213	0.25	11.9	81.8	0.25	5.835	29.64	12.1	58.83
S. aureus ATCC Smith	0.5	11.4	39.3	0.25	10.44	51.13	64	302.51
S. aureus ATCC 33591	0.5	13.6	46.3	0.5	6.42	16.19	23.81	56.61
S. aureus CA-MRSA MW2	0.25	8.88	62.5	0.5	9.39	23.12	22.035	52.49
S. aureus CA-MRSA R2527 tetR	0.25	5.02	37.8	0.5	8.77	21.68	26.16	62.06
S. aureus 6538P				0.25	4.215	22.05	9.97	48.95
S. aureus ATCC 25923				0.25	4.36	22.71	12.7	61.63
S. aureus WIS-1				0.5	5.4	13.80	17.725	42.48
S. aureus LSI 1848				0.5	8.22	20.41	26.5	62.86
S. aureus 307109				0.5	6.56	16.52	13.285	32.17
***S. aureus* Mean**		**10.2 ± 3.3**	**53.5 ± 18.6**		**6.96**	**23.73 ± 10.61**	**22.83**	**78.06 ± 79.47**
S. pneumoniae ATCC 10813	0.06	0.900 1.02	25.4 28.8	0.06	2.25	53.36	3.765	83.01
S. pneumoniae ATCC 49619	0.06	0.799	22.6	0.06	0.495	17.53	1.115	30.40
S. pneumoniae CDC 1020 tetR	0.06	1.25	35.3	0.12	2.71	31.20	4.875	52.35
S. pneumoniae CDC 1199 tetR	0.03	0.368	20.8	0.06	1.145	31.00	2.885	65.78
S. pneumoniae CDC 1293 tetR	0.06	1.45	38.7	0.12	2.905	33.13	7.4	77.03
S. pneumoniae CDC 1329	0.03	0.561	31.7					
S. pneumoniae CDC 1396 tetR	0.06	0.820	23.2					
S. pneumoniae CDC 146	0.06	0.798	22.6					
S. pneumoniae CDC 673	0.03	0.408	23.1					
S. pneumoniae CDC 1325 tetR	0.06	0.636	19.1					
S. pneumoniae ATCC 6301	0.03	0.540	30.5					
S. pneumoniae ATCC 6303	0.06	0.526	14.9					
***S. pneumoniae* Mean**		**0.759 ± 0.330**	**23.8 ± 9.6**		**1.9**	**33.25 ± 12.85**	**4.005**	**61.71 ± 21.05**
E. coli ATCC 25922	0.5	7.03	25.3	0.5	41.82	98.84	NA	NA
E. coli 1-741 tetR	0.5	5.86	21.6	0.5	32.38	76.53	NA	NA
E. coli 1-894 tetR	0.5	6.00	22.0	1	23.88	28.39	37.81	44.68
E. coli 681				1	44.705	52.83	NA	NA
K pneumoniae ATCC 43816	2.0	71.1 77.8	59.4 65.0					
Enterobacteriaceae Mean		**23.3 ± 34.1**	**32.8 ± 19.7**		**35.695**	**64.14 ± 30.35**		

[a] Calculated from Static Dose (mg/kg/24h) presented in original report.

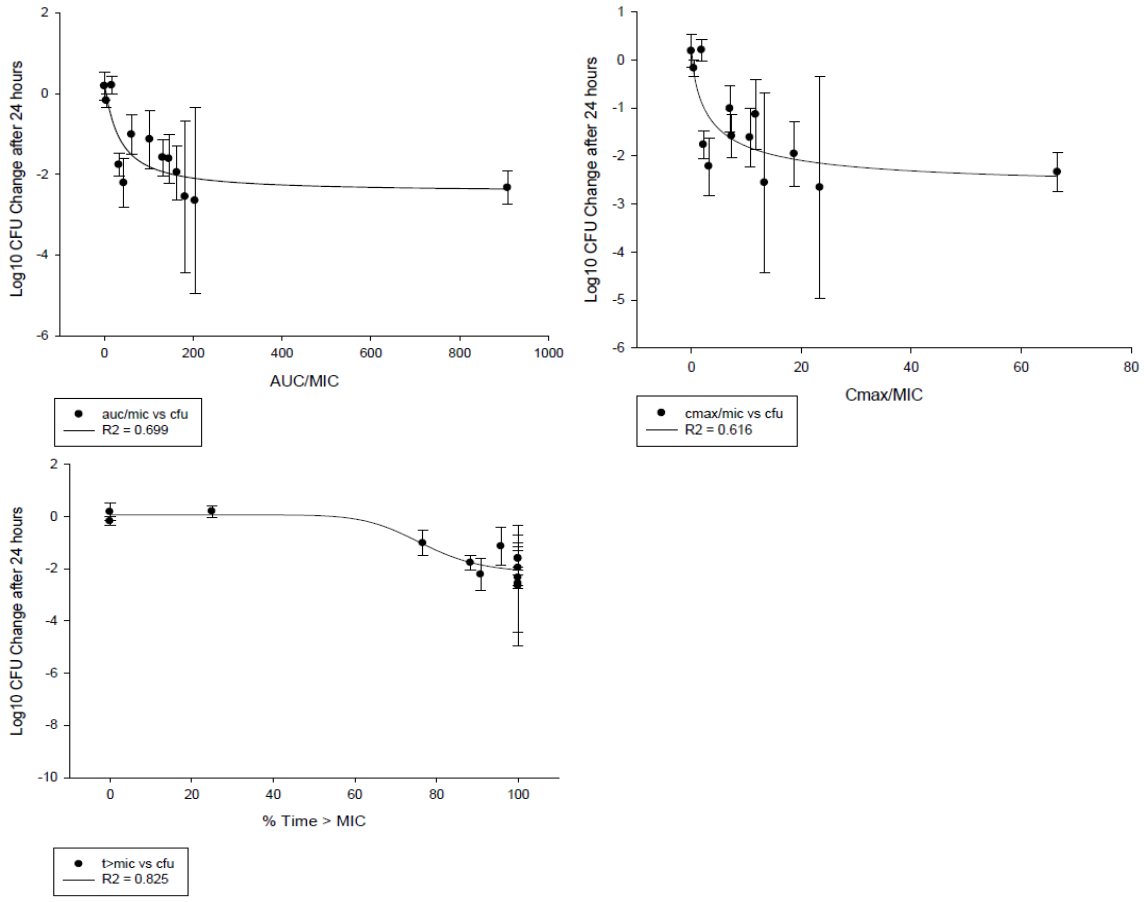
ATCC = American Type Culture Collection, AUC = area under the plasma concentration time curve, CFU = colony-forming units, MIC = minimum inhibitory concentration.
Source: adapted from applicant's Summary of Clinical Pharmacology Studies – Special Studies – Microbiology.

Mouse neutropenic lung model

In an initial study (report Nicolau C370), neutropenic mice were inoculated nasally with test strain (1 pen^R *mefA+ S. pneumoniae* #100 and 1 pen^S SPN #22; 6 test animals per strain), before being administered fractionated SC omadacycline doses of between 0.25 and 25 mg/kg (dosing intervals 6, 12 or 24 hours), although the tested regimens varied (inexplicably) for each strain, resulting in little to no fractionation practice amongst the assays for SPN #22.

The report states that a high correlation between the plasma free drug AUC/MIC and efficacy was noted for both strains, however the reported R^2=0.904 and 0.699, respectively, suggests this relationship was somewhat less robust for SPN #100:

Figure 2. Relationship between plasma free drug AUC/MIC and antimicrobial activity of omadacycline against *S. pneumoniae* #100 in the neutropenic mouse lung model (Nicolau C370)



Source: submitted report Nicolau C370, Figure 3.

Lepak *et al.* (2017) also reported dose-response data for 4-fold increasing SC doses ranging from 0.1 to 25.6 mg/kg/12h omadacycline against 4 *S. pneumoniae* test strains in the neutropenic mouse lung model. The relationships for plasma AUC/MIC and ELF AUC/MIC were moderately robust (R^2=0.74 and 0.75, respectively). The unusually high values obtained for strain 1293 are not explained.

Table 18. 24-h static and 1-log and 2-log kill doses and associated plasma free drug AUC/MIC values for *S. pneumoniae* (4 strains) in the neutropenic mouse lung model (Lepak 2017)

S. pneumoniae strain	24-h growth in untreated control animals (log_{10} CFU/lungs)	MIC (mg/liter)	Stasis			1-log_{10} kill			2-log_{10} kill		
			24-h total dose (mg/kg)	Plasma AUC/MIC	ELF AUC/MIC	24-h total dose (mg/kg)	Plasma AUC/MIC	ELF AUC/MIC	24-h total dose (mg/kg)	Plasma AUC/MIC	ELF AUC/MIC
1293	2.34	0.06	1.28	19.83	17.80	18.24	179.98	200.64	NA[a]		
10813	1.64	0.06	0.92	15.79	14.18	1.26	19.66	17.61	1.81	25.05	23.19
140	1.13	0.125	NC[b]			0.71	6.06	6.00	3.06	18.65	17.26
49619	0.85	0.03	NC			0.45	15.21	13.31	2.12	56.20	47.27

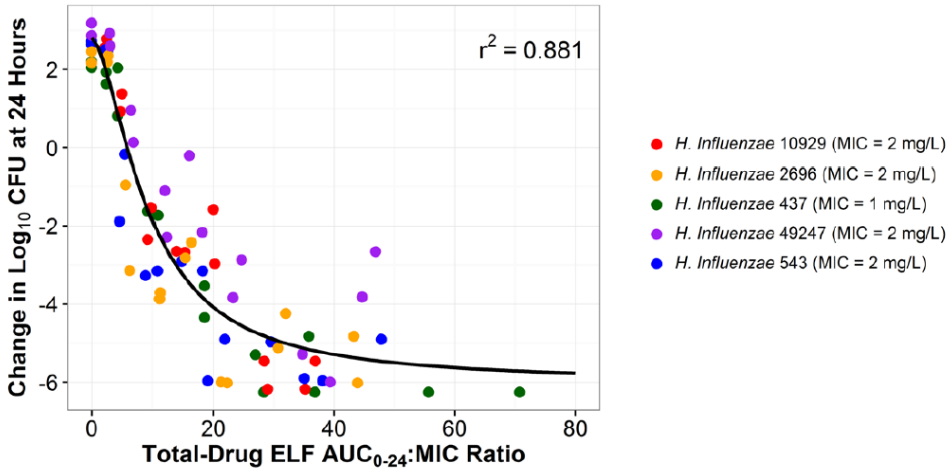
[a]NA, endpoint not achieved.
[b]NC, not calculated.

Source: Lepak *et al.* (2017) Table 2.

One-compartment *in vitro* model

The total-drug ELF AUC0-24:MIC ratio associated with efficacy against a panel of 5 clinical *H. influenzae* isolates (omadacycline MIC 1 to 2 µg/mL) was determined in a dose-ranging study in a one-compartment *in vitro* infection model delivering 24-hour omadacycline concentration-time profiles representing those observed in human epithelial lining fluid (ELF) after IV administration of q12h doses from 12.5 to 400 mg. The target selected to be used in PTA analysis was the median ELF AUC_{0-24}:MIC ratio corresponding to 1-log kill AUC/MIC = 8.91.

Figure 3. Relationship between change in log10 CFU/ml from baseline at 24 hours and omadacycline total-drug ELF AUC:MIC ratio for *H. influenzae* (5 strains) in the one-compartment *in vitro* model (ICPD-00396)



Source: applicant's submitted report ICPD-00396.

3.3.2.12. Probability of target attainment analyses

The applicant performed Monte Carlo Simulation to assess the probability of target attainment with four different dosing regimens. The popPK model is discussed in section 3.3.1. Pharmacokinetics.

Univariable analysis

Clinical PK/PD relationships for efficacy were explored for both CABP and ABSSSI using data from Phase 3 patients in the Microbiologically-Evaluable (ME) population who had PK data available, for each indication (182 subjects and 10 subjects for ABSSSI and CABP, respectively).

The only significant univariable relationship identified was between AUC/MIC and ECR (p=0.011) in the subset of ABSSSI subjects with *S. aureus* at baseline. Model-predicted percent probability of clinical

success at ECR in ABSSSI ranged from 87.2 to 95.6% for *S. aureus* up to MIC 0.5 µg/mL, when clinical response at ECR was modelled as a continuous, two-group (free AUC:MIC threshold 13.2) or three-group (free AUC:MIC thresholds 14.5 and 70.9) variable.

PTA analysis

For ABSSSI, non-clinical PK-PD targets were initially selected based on the median plasma free drug AUC/MIC ratio targets associated with stasis for *S. aureus, S. pneumoniae* (use to inform targets for *Streptococcus* spp.), and *E. coli*, in the neutropenic mouse thigh model (Andes Thigh 2017). For CABP, PK-PD targets were initially selected based on the median free-drug ELF AUC/MIC ratio targets associated with a 1- $\log_{10}$ CFU reduction from baseline for *S. pneumoniae* in the neutropenic mouse lung model (Lepak 2017), excluding isolate 1293, and for *H. influenzae* in a 24-hour one-compartment *in vitro* infection model.

Table 19. Omadacycline free-drug plasma and ELF AUC/MIC targets selected by the Applicant for PTA analysis

Organism	Median Static Plasma AUC/MIC	Median 1 log kill ELF AUC/MIC
ABSSSI		
***S. aureus* (10)**	**21.9**	
***S. pneumoniae* (5)**	**31.2**	
***E. coli* (4)**	**64.7**	
CABP		
***S. pneumoniae* (3)**		**13.3**
***H. influenzae* (5)**		**8.91**

ELF = epithelial lining fluid. Source data: submitted report ICPD-00398-1.

The applicant performed target attainment analyses for both ABSSSI and CABP using AUC/MIC ratio targets randomly assigned based on an estimated truncated log normal distribution of AUC/MIC ratio targets for each pathogen. The observed mean and standard deviation among the non-clinical PK-PD targets were used as the parameters for the log normal distributions. Such an approach, while appropriate for some types of analysis (e.g. popPK), is less desirable from the regulatory standpoint for PTA analyses, where the primary concern is adequate coverage of the least susceptible target organisms when they are eventually encountered in clinical practice. At the request of CHMP, PTA analysis was also run using the median, highest and second highest (excluding high outlier for *S. pneumoniae*) targets observed in non-clinical models for the key organisms for the CAP indication (*S. pneumoniae* and *H. influenzae*).

The breakpoints used to interpret the PTA analysis results were MIC90 values from European SENTRY surveillance data. The MIC90 values from the presented European surveillance data for *S. aureus* and *S. pneumoniae* reflect the breakpoints agreed so far with EUCAST (further discussion re: *H. influenzae* is to follow).

ABSSSI

S. aureus

Both iv-to-po and po dosing regimens with a loading dose (either 100 mg q12h or 200 mg q24h on Day 1 for iv loading) provided >90% PTA on Days 1 to 2 and switch day, using randomly-assigned free-drug plasma AUC:MIC targets, only up to MIC 0.12 µg/mL. At the European surveillance 2016 MIC90 value/ EUCAST breakpoint for *S. aureus* of 0.25 µg/mL, PTA was as low as 60.8% for the po dosing regimen. When assessed against the European surveillance 2016 distribution for *S. aureus* there was a >90% PTA for iv-to-po (100 mg iv q12h) and 86.9% probability of PTA for po dosing regimen.

Streptococcus species

Similarly, the probability of achieving stasis for *S. pneumoniae* was >90% at the European surveillance 2016 MIC90/ EUCAST breakpoint value for *S. pneumoniae* (proxy) 0.12 µg/mL, but only for the for the "IV-to-PO" dosing regimens with loading dose.

The Applicant has not conducted re-analyses for *S. aureus* or *Streptococcus* species using median and highest target values. Given the sufficient evidence for good clinical outcomes in ABSSSI, further discussion of the PTA support for this indication is not pursued.

CAP

S. pneumoniae

Both iv-to-po and po dosing regimens with a loading dose (either 100 mg q12h or 200 mg q24h on Day 1 for iv loading) provided >90% PTA on Days 1 to 2 and switch day, at the European surveillance 2016 MIC90 value/ EUCAST breakpoint for *S. pneumoniae* of 0.12 µg/mL, using both randomly-assigned total-drug ELF AUC:MIC targets and randomly-assigned free-drug plasma AUC:MIC targets. When assessed against the European surveillance 2016 distribution for *S. pneumoniae* there was a >99% PTA for all dosing regimens for both total-drug ELF and free-drug plasma AUC:MIC ratios.

As expected, PTA using a single conservative target (highest observed) was lower than PTA using randomly assigned or median targets for *S. pneumoniae* and does not cover the European surveillance 2016 MIC90/ EUCAST breakpoint in either ELF or plasma. As noted by the Applicant, these predictions do not agree with the clinical efficacy data from study CABP-1200, in which higher MIC values were successfully treated. Furthermore, PTA using the second highest observed (excluding *S. pneumoniae* 1293 as an outlier) achieved >90% coverage up to the same MIC value as median target or a randomly assigned target, that is to say the three approaches produced the same highest MIC value with >90% coverage.

H. influenzae

Iv-to-po regimens with a loading dose provided >90% PTA on Days 1 to 2 and switch day, at the European surveillance 2016 MIC90 value for *H. influenzae* of 1 µg/mL, using randomly-assigned total-drug ELF AUC:MIC targets. Meanwhile, PTA for the po regimen at the same MIC was 82.7%. PTA was notably lower for randomly-assigned free-drug plasma AUC:MIC targets. At the European surveillance 2016 MIC90 value of 1 µg/mL, PTA for plasma targets was as low as 35.0% for the po dosing regimen. When assessed against the European surveillance 2016 distribution for *H. influenzae* there was a >89.9% PTA for iv-to-po (100 mg iv q12h) and 86.1% probability of PTA for po dosing regimen, but only using total-drug ELF.

PTA using a single conservative target (highest observed) for *H. influenzae* achieved >90% coverage up to the same MIC value as median target or a randomly assigned target. Adequate coverage is achieved at a higher MIC (covering the European surveillance 2016 MIC90) for ELF targets than plasma targets (not reaching the European surveillance 2016 MIC90). Notably, there is better agreement between clinical efficacy data for *H. influenzae* and the PTA results for ELF targets than plasma targets, which is interesting.

There appears to be a disconnect (in favour of clinical outcomes) between the non-clinical predictions and clinical outcomes observed in study CABP-1200. The Applicant asserts that this indicates that the highest plasma PK-PD target is not a good predictor of clinical outcome for in the CABP-1200 study. However, this lack of agreement weakens rather than strengthens the available evidence for efficacy in CAP, which comes from a single pivotal study. Given the conclusion that a positive B/R balance cannot be concluded for omadacycline in CAP without additional data from a further study, additional

discussion regarding the PTA support for this indication does not need to be further pursued at this time.

Table 20. Percent probabilities of PK-PD target attainment by MIC based on randomly assigned plasma or ELF AUC/MIC ratio targets associated with stasis for *S. aureus* and *Streptococcus* species, among simulated patients after administration of IV to PO or PO omadacycline dosing regimens

MIC (mg/L)	IV to PO dosing regimen						PO dosing regimen	
	With IV loading dose			Without IV loading dose			With PO loading dose	Without PO loading dose
	100 mg IV q12h on Day 1 followed by 100 mg IV q24h on Days 2 or 3 with a PO switch to 300 mg PO q24h on Days 3 or 4			100 mg IV q24h on Days 1-2 or 1-4 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	300 mg PO q24h on Days 1 and 2
	Days 1 to 2[c]	Day of PO switch[d]		Days 1 to 2[c]	Day of PO switch[d]		Days 1 to 2[c]	
		Day 3	Day 5		Day 3	Day 5		
***S. aureus* (ABSSSI)** – net stasis								
0.06	100	100	100	100	99.9	100	99.7	98.2
0.12	100	98.9	98.2	99.0	96.6	97.5	94.8	80.8
0.25	91.3	71.7	68.2	61.0	59.1	62.9	60.8	32.4
0.5	35.1	18.5	16.0	6.52	10.3	12.6	15.7	4.08
***Streptococcus* spp. (ABSSSI)** – net stasis								
0.03	100	100	100	100	100	100	100	99.6
0.06	100	99.9	99.7	99.9	99.4	99.6	98.3	92.7
0.12	99.1	91.6	89.4	88.3	84.0	86.6	82.9	59.2
0.25	66.4	44.2	40.5	30.3	31.9	35.4	36.6	14.0

a Target value randomly assigned based on an estimated log normal distribution of PK-PD targets associated with the same endpoint in the same species.
b. Shaded cells indicate PK-PD target attainment values ≥90%.

Table 21. Clinical Response (CABP-1200 study) and Percent Probabilities of PK-PD Target Attainment by MIC for Total-drug ELF or Free-drug Plasma AUC:MIC Ratio Targets Associated with a 1-log_{10} CFU Reduction for *S. pneumoniae*, Simulated Patients, Omadacycline 100 mg iv q12h on Day 1 Followed by 100 mg iv q24h on Day 2 with a po Switch to 300 mg po q24h on Day 3

		Percent probability of PK-PD target attainment by MIC on Days 1 to 2 among simulated patients[b,c]							
		Assessment of total-drug ELF exposures and AUC:MIC ratio targets				Assessment of free-drug plasma exposures and AUC:MIC ratio targets			
MIC (mg/L)	Percentage of clinical success at PTE (n/N), N=28[a]	Randomly assigned based on all PK-PD targets, excluding the outlier[d]	Median of all PK-PD targets, excluding the outlier[e]	Highest PK-PD target, including the outlier[f]	Second highest PK-PD target, including the outlier[g]	Randomly assigned based on all PK-PD targets, excluding the outlier[d]	Median of all PK-PD targets, excluding the outlier[e]	Highest PK-PD target, including the outlier[f]	Second highest PK-PD target, including the outlier[g]
0.015	100 (2/2)	100	100	100	100	100	100	100	100
0.03	85.7 (12/14)	100	100	100	100	100	100	**99.5**	100
0.06	100 (10/10)	100	100	**98.5**	100	100	100	26.0	100
0.12*	50 (1/2)	100	100	15.0	100	100	100	0	100
0.25	NA	100	100	0	100	**97.5**	**100**	0	**99.9**
0.5	NA	**99.3**	100	0	**100**	75.4	85.2	0	42.2
1	NA	82.9	**96.3**	0	67.0	34.3	0.96	0	0.02

a. Based on data from patients with *S. pneumoniae* at baseline in the microITT population of Study PTK0796-CABP-1200.
b. Assessed using total-drug ELF or a free-drug plasma AUC:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline for *S. pneumoniae* based on data from a neutropenic murine lung-infection model.
c. Based on the assessment of average total-drug ELF or free-drug plasma AUC_{0-24} on Days 1 and 2.
d. Based on data for all *S. pneumoniae* isolates excluding the outlier (*S. pneumoniae* 1293), the total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC:MIC ratio targets associated with the same endpoint.
e. Based on data for all *S. pneumoniae* isolates excluding the outlier (*S. pneumoniae* 1293), the median total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline were 13.3 and 15.2, respectively.
f. Based on data for all four *S. pneumoniae* isolates studied, the highest total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline were 200.6 and 180.0, respectively.
g. Based on data for all four *S. pneumoniae* isolates studied, the second highest total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline were 17.6 and 19.7, respectively.
*European surveillance 2016 MIC90.

Table 22. Clinical Response (CABP-1200 study) and Percent Probabilities of PK-PD Target Attainment by MIC for Total-drug ELF or Free-drug Plasma AUC:MIC Ratio Targets Associated with a 1-log_{10} CFU Reduction for *H. influenzae*, Simulated Patients, Omadacycline 100 mg iv q12h on Day 1 Followed by 100 mg iv q24h on Day 2 with a po Switch to 300 mg po q24h on Day 3

		Percent probability of PK-PD target attainment among simulated patients[b,c]							
		Assessment of total-drug ELF exposures by AUC:MIC ratio targets				Assessment of free-drug plasma exposures by AUC:MIC ratio targets			
MIC (mg/L)	Percentage of Clinical Success at PTE (n/N), N=32[a]	Randomly assigned based on all PK-PD targets[d]	Median of all PK-PD targets[e]	Highest PK-PD target[f]	Second highest PK-PD target[g]	Randomly assigned based on all PK-PD targets[d]	Median of all PK-PD targets[e]	Highest PK-PD target[f]	Second highest PK-PD target[g]
0.25	NA	100	100	100	100	100	100	100	100
0.5	100 (1/1)	100	100	100	100	**99.5**	**100**	**99.0**	**99.9**
1*	88.9 (16/18)	**99.5**	**100**	**99.2**	**99.9**	67.0	61.2	16.2	44.2
2**	66.7 (8/12)	68.8	65.1	19.0	48.6	7.36	0.14	0	0.02
4	100 (1/1)	8.42	0.22	0	0.04	0	0	0	0

a. Based on data from patients with *H. influenzae* at baseline in the microITT population of Study PTK0796-CABP-1200.
b. Assessed using total-drug ELF or a free-drug plasma AUC:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline for *H. influenzae* based on an one-compartment *in vitro* infection model were randomly assigned based on an estimated log normal distribution of AUC:MIC ratio targets associated with the same endpoint.
c. Based on the assessment of average total-drug ELF or free-drug plasma AUC_{0-24} on Days 1 and 2.
d. Based on data for all five *H. influenzae* isolates, the total-drug ELF or free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline were randomly assigned based on an estimated log normal distributions of AUC:MIC ratio targets associated with the same endpoint.
e. Based on data for all five *H. influenzae* isolates, the median total-drug ELF or free-drug plasma AUC:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline was 8.91.
f. Based on data for all five *H. influenzae* isolates studied, the highest total-drug ELF or free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline was 11.6.
g. Based on data for all five *H. influenzae* isolates studied, the second highest total-drug ELF or free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline was 9.73.

*European surveillance MIC90 using 2016 data, **European surveillance MIC90 using 2009-2016 data, see Q193.

Susceptibility breakpoints

EUCAST have suggested susceptible breakpoints based on ECOFF and PTA data for *S. aureus* (≤0.25 mg/L), *S. lugdunensis* (≤0.25 mg/L*), S. pneumoniae* (≤0.125 mg/L), *S. agalactiae* (≤0.25 mg/L), *S. pyogenes* (≤0.25 mg/L), *S. anginosus* group (≤0.125 mg/L) and H. influenzae (≤2 mg/L).

The committee did not agree there was sufficient evidence to set breakpoints for additional species (*Enterococcus* spp., *Enterobacterales* and anaerobes).

3.3.3. **Discussion on clinical pharmacology**

ADME

Biopharmaceutical data indicate a rather pronounced food effect, which has been adequately characterised.

Omadacycline has been shown to be metabolically stable both in vivo and in vitro. 25-45% of omadacycline's total clearance is due to renal excretion mechanisms. Urinary clearance (CLr) following iv administration was estimated in several studies at 3 L/h. Renal filtration is estimated to be approximately 6 L/h. Consequently, renal reabsorption via active transport seems a possibility. Biliary excretion of unchanged drug constitutes the remainder, ca 55-75% of total clearance. Across iv studies, total clearance was around 10 L/h, and terminal half-life 15-25 h. Daily dosing results in accumulation of approximately 50% over the initial dose exposure.

Special populations

One study was performed to evaluate the effect of renal function on omadacycline exposure. The results did not indicate any impact on omadacycline AUC in the ESRD group.

Regarding the effect of decreased hepatic function, a dedicated hepatic impairment study including both oral and iv omadacycline did not show a difference in AUC across the different cohorts; healthy subjects, Child Pugh classes A, B and C.

Interactions

Effect of other medicines on omadacycline:

The risk for clinically relevant PK interactions is deemed low based on the available data. Some uncertainty still remains though for a possible scenario where omadacycline turns out to be a substrate for a transport protein involved in its biliary secretion. Some transport protein substrate assays (OTP1B1 and 1B3) are requested to be repeated as several concentrations of the possible substrate is recommended to be tested. In the performed studies, only one concentration of omadacycline was used. **PAM**

Effect omadacycline on other medicines:

Omadacycline is deemed to have low potential as perpetrator in PK interactions. No competitive CYP inhibition is expected in vivo based on the in vitro assay. The same conclusion may be drawn for CYP induction. TDI data for all CYPs has not been presented and is requested. **LoQ** For the transport protein perpetrator assays, some uncertainty remain regarding if the results should be seen as valid as the studied concentration range may have been too low in comparison with regulatory cut-offs and new studies are requested. **PAM**

MoA

The mechanism of action and pharmacological properties of omadacycline have been generally well characterised through a series of in vitro studies. The data presented describing laboratory selection of resistance is sparse. Resistance was not detected in any isolate in the Phase 3 studies, in any of the Phase 3 trials, although the Applicant acknowledges that collection of post-baseline isolates, and therefore the opportunity to detect on-treatment resistance emergence, was limited.

PK/PD index

It appears that AUC/MIC is the most relevant index, as for other tetracyclines.

PD target

The data underpinning selection of the target are sparse and highly variable. The lack of positive control means there is no clear bridge or comparison possible between results of the different models. At the request of CHMP, the Applicant has presented PTA analyses using randomly assigned, median, highest and second highest (excluding high outlier) targets for key pathogens for CABP. The same re-analysis have not been produced for ABSSSI.

PTA analysis

The Applicant's emphasis on the clinical PDT (ECR), given that this clinical PK/PD relationship is based upon a very small number of clinical failures in the clinical trials, the role of other factors (such as adjunctive surgery) is unclear, and the relationship does not relate to the primary efficacy endpoint required by EMA.

The applicant also emphasises the important of ELF over plasma free drug AUC/MIC targets in CABP, however, the values for ELF penetration in both non-clinical studies and healthy volunteer human PK studies show high inter-individual variability that may, in part, be an artefact of the sampling approach.

A significant proportion of CABP patients had infections caused by atypical infections, coverage of which cannot be addressed by PTA analysis due to the lack of established non-clinical models for characterising PK-PD relationships in these species. Evidence for efficacy in atypical pathogens is addressed in section 3.3.5. Clinical efficacy.

Notwithstanding the above, the presented PTA results are not favourable for the highest MIC values of interest across all key pathogens and cannot, therefore, support efficacy of the dosing regimen used in the Phase 3 pivotal studies, nor inclusion of all the species proposed by the Applicant for the list of organisms in SmPC 5.1 expected to be susceptible on the basis of *in vitro* data. There appears to be a disconnect (in favour of clinical outcomes) between the non-clinical predictions and clinical outcomes observed in study CABP-1200, in which organisms with higher MIC values than those predicted by PTA analysis were successfully treated. The Applicant considers that nonclinical PK-PD PTA data may not be as predictive for certain classes of antibiotics (tetracyclines for instance).

3.3.4. **Conclusions on clinical pharmacology**

Regarding PK, the applicant has agreed to perform three studies post approval, which is deemed to be an acceptable approach. The studies are:

1) in vitro transport substrate studies for the transporters OATP1B1 and OATP1B3
2) in vitro CYP3A4 and CYP2C9 inhibition assessment at the theoretical maximal gut concentration
3) in vitro inhibition evaluation of the transporters OAT1, OAT3, P-gp and BCRP

There is also one remaining question in the LoQ where The applicant is requested to fulfil the guideline requirements and provide in vitro data on TDI for CYP2B6, 2C8 and 2C19.

Otherwise, all PK related issues are resolved.

Overall, given the sufficient evidence from two adequately-sized clinical studies for good clinical outcomes in ABSSSI at suitable MIC values, further discussion of the lack of comprehensive PTA support for this indication is not pursued. Furthermore, given that a positive BR balance cannot be concluded for omadacycline in CAP without additional data from a further study, additional discussion regarding the PTA support for this indication does not need to be further pursued at this time.

3.3.5. **Clinical efficacy**

Table 23. Overview of Pivotal and Supportive Efficacy Studies

Study ID	N study centres	Design	Study Posology	Primary Study Objective	N per am arm	N total	Duration	M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint
Studies in cSSSI										
PTK0796-CSSI-0702	11 (US)	Phase 2, R, SB, active comparator	Omadacycline 100mg iv q24h → 200mg po q24h; Linezolid 600mg iv q12h → 600mg po q12h	Safety and tolerability vs linezolid in adults with cSSSI	Omadacycline=111 Linezolid=108	219	Up to 7d IV, up to 14d total (iv+po)	56%M 45y	cSSSI (major abscess, infected lower extremity ulcer, cellulitis, infection associated with trauma or removable foreign body)	IACR at TOC visit in mITT and CE-TOC
PTK0796-CSSI-0804[a]	6 (US)	Phase 3, R, SB, active comparator	Omadacycline 100mg iv q24h → 300mg po q24h; Linezolid 600mg iv q12h → 600mg po q12h	Non-inferiority to linezolid in adults with cSSSI	Omadacycline=68 Linezolid=72	143	Up to 7d IV, up to 14d total (iv+po)	66%M 39y	cSSSI (major abscess, cellulitis, infection associated with trauma or removable foreign body) + evidence of SIR, immunosuppression or specified comorbidity	IACR at EOT and TOC visit in ITT and CE
Studies in ABSSSI										
PTK0796-ABSI-1108	55 (N. America, E. Europe, W. Europe, Latin America)	Phase 3, R, DB, active comparator	Omadacycline 100mg iv q12h x2 iv q24h → 300mg po q24h; Linezolid 600mg iv q12h → 600mg po q12h	Non-inferiority to linezolid in adults with ABSSSI	Omadacycline=329 Linezolid=326	645	Up to 7d IV, up to 14d total (iv+po)	65%M 47y	ABSSSI ≥75cm^2 (wound infection, cellulitis/erysipelas, major abscess) + evidence of SIR	Overall clinical response at PTE visit in mITT and CE
PTK0796-ABSI-16301	33 (US)	Phase 3, R, DB, active comparator	Omadacycline 450mg po q24h x2 then 300mg po q24h; Linezolid 600mg po q12h	Non-inferiority to linezolid in adults with ABSSSI	Omadacycline=368 Linezolid=367	735	7d 14d po	63%M 44y	ABSSSI ≥75cm^2 (wound infection, cellulitis/erysipelas, major abscess) + evidence of SIR	Overall clinical response at PTE visit in mITT and CE
Studies in CABP										
PTK0796-CABP-1200	86 (N. America, W. Europe, E. Europe, Rest of	Phase 3, R, DB, active comparator	Omadacycline 100mg iv q12h x2 then q24h → 300mg po q24h; Moxifloxacin 400mg iv q24h	Non-inferiority to moxifloxacin in adults with CABP Port Risk Class III-IV	Omadacycline=329 Moxifloxacin=331	660	Up to 7d IV, up to 14d total (iv+po)	56%M 62y	Radiographically confirmed CABP requiring iv Abx, PORT Risk Class II-IV	Overall clinical response at PTE visit in ITT and CE

	world)		→ 300mg po q24h							

ABSSSI=acute bacterial skin and skin structure infection, CABP=community-acquired bacterial pneumonia, cSSSI=complicated skin and skin structure infections, IACR=investigator's assessment of clinical response, R=randomised, SB=single-blind, TOC=test of cure, PTE=post therapy evaluation, SIR=systemic inflammatory response, mITT=modified intent to treat, CE=clinically evaluable,

[a] Terminated early by sponsor. Table compiled by assessor. Source data: applicant's submitted Summaries of Clinical Efficacy Studies in ABSSSI and CABP.

3.3.5.1. Dose response studies

No dose response studies were conducted for the proposed indications. Dose selection for the Phase 3 programme was based on *in vitro* and *in vivo* non-clinical PK/PD studies and Monte Carlo simulations of pharmacodynamic target attainment (see section 3.3.2. Pharmacodynamics).

The proposed iv loading dose of 200 mg q24h was not tested in PTA analysis or in clinical studies of ABSSSI or CABP, but only in patients with uncomplicated UTI in study PTK0796-UUTI-15103, thus there is no substantial safety database for it in the target populations.

In Study PTK0796-UUTI-15103, a median increase in heart rate of 20 bpm was seen after administration of an iv loading dose of 200-mg over 30-45 minutes. A median increase of 20 bpm is considered potentially clinically significant for the target patient populations, who are generally more clinically unwell than patients with uUTI and may not tolerate this haemodynamic change well. No additional details are provided to enable further characterisation of any potential safety concern e.g. timing and speed of onset of the effect, time of resolution/ duration of the effect, related changes (if any) in blood pressure, TEAEs reported in association.

The Applicant asserts, on the basis of modelling, that infusing the 200 mg dose over a 60-90 minutes will reduce median heart rate elevations to below 20 beat per minute. However, there are no clinical data to support this hypothesis. Support for the safety of the alternative iv loading dose of 200 mg in the target populations is insufficient to preclude its recommendation in section 4.2. In addition, there is no clearly established benefit demonstrated in terms of clinical efficacy. The alternative iv loading dose is therefore not considered acceptable for inclusion in the product information.

3.3.5.2. Main studies

3.3.5.2.1. Study PTK0796-ABSI-1108 - *A Phase 3 Randomised, Double-Blind, Multi-Centre Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Linezolid (Zyvox®) IV/PO for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)*

Methods (Study PTK0796-ABSI-1108)

- **Study participants**

Subjects 18 to 80 years of age from 55 global centres, with qualifying ABSSSI ≥75 cm^2 continuous surface area (SA), expected to require at least 3 days' IV treatment:

- 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.

And one of the following, within 24h of randomisation:

- Elevated white blood cell (WBC) count (≥ 10,000 cells/mm3) or leukopenia (≤ 4,000 cells/mm3);

- 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]).

Subjects were stratified at entry by ABSSSI type and geographic area, and major abscess was limited to 30% of subjects.

Principal exclusion criteria:

(a) having received 1 or more dose of potentially effective systemic antibiotic in the 72 h prior to the first dose of test article (unless infecting organism shown to be intermediate or resistant to initial treatment),

(b) having applied a topical antibacterial agent(s) continuously for ≥72 h immediately prior to randomisation,

(c) infections were there outcome was strongly influenced by other factors, where treatment >14 days was anticipated, when chronic skin lesions impaired determination of response, where the pathogen was suspected or known to be resistant to test article (e.g. chronic >3 months, underlying skin condition, burns, life-threatening infections (necrotising fasciitis, gangrene), underlying vascular insufficiency requiring immediate revascularisation or curative amputation, bone, joint or other organ involvement, underlying immune deficiency, human or animal bites).

(d) Pre-existing hepatic, renal, immunological or cardiac disease as defined in the protocol

(e) Haemodynamically unstable despite fluid resuscitation, or requiring pressor agents

(f) Receipt of MOA inhibitor within 14 days prior to screening

- **Treatments**

Subjects were randomised (1:1) to one of the following two treatments, for up to 7 days IV and up to 14 days total IV+PO:

- Omadacycline, 100 mg iv q12h for 2 doses, then 100 mg iv q24h with the option to switch to 300 mg po q24h after a minimum of 3 days.
- Linezolid, 600 mg iv q12h with the option to switch to 600 mg po q12h after a minimum of 3 days.

Subjects could receive adjunctive Gram-negative cover at the discretion of the investigator if a Gram-negative pathogen, anaerobe or linezolid-resistant pathogen was detected at baseline.

- **Objectives**

Primary objective: to demonstrate that omadacycline administered iv and po was non-inferior to linezolid administered iv and po in the treatment of adults with ABSSSI known or suspected to be due to Gram-positive pathogens.

Secondary objectives:

- to evaluate the safety of omadacycline in adults subjects with ABSSSI.
- to evaluate the clinical response according to the causative pathogen.
- to characterise the PK of omadacycline in adults subjects with ABSSSI.

- **Outcomes/endpoints**

Structured evaluations were conducted at Early Clinical Response (48-72 h after first dose), End of Treatment (EOT, within 2 d of last dose) and Post Therapy Evaluation (PTE, 7-14 d after last dose).

Co-primary efficacy endpoints: Overall clinical response at PTE (derived from IACR at EOT and PTE) in the mITT and CE-PTE populations, according to the following criteria:

Table 24. Investigator-assigned clinical success/ failure at the EOT and PTE visits

Clinical Success at the EOT and PTE assessments was defined as meeting the following:
- The subject was alive.
- The infection was sufficiently resolved such that further antibacterial therapy was not needed. These subjects may have had some residual changes related to infection requiring ancillary (ie, non-antibiotic) treatment, eg, bandages on a healing wound, debridement of uninfected tissue (ie, necrotic).

Clinical Failure was defined as meeting any of the criteria below:
- The investigator discontinued test article and indicated that the infection had responded inadequately such that alternative (rescue) antibacterial therapy was needed.
- The subject received antibacterial therapy that may have been effective for the infection under study for a different infection from the one under study.
- The subject developed an AE that required discontinuation of test article prior to completion of the planned test article regimen.
- An unplanned major surgical intervention (ie, procedures that would not normally be performed at the bedside) for the infection under study.
- The subject died before evaluation.

Indeterminate was defined as the clinical response to test article could not be adequately inferred because:
- The subject was not seen for the assessment because the subject withdrew consent, was lost to follow-up, or other specified reason.
- Other specified reason.

Source: applicant's Summary of Clinical Efficacy – ABSSSI.

Secondary efficacy endpoints:

- Microbiological response at EOT and overall microbiological response at PTE (derived from microbiological response at EOT and PTE) per-subject in the micro-mITT and ME-PTE populations.
- Overall microbiological response at PTE (derived from microbiological response at EOT and PTE) according to pathogen in the micro-mITT and ME-PTE populations.

Infection site or blood isolates always considered a pathogen were: MSSA, MRSA, Group A, B,C and G β-haemolytic streptococci, *Streptococcus anginosus* group, *E. faecalis* and *E. faecium*, *Staphylococcus lugdunensis*. Isolates always considered contaminants were: fungi, *Staphylococcus saprophyticus*, *Corynebacterium* spp., *Bacillus* spp., diptheroids, *Micrococcus* spp., and *Propionibacterium* spp.. Other isolates and combinations were considered in a blinded case-by-case- manner.

- **Sample size**

Assuming an 85% outcome rate in both treatment groups, non-inferiority margin of 10%, and a 1-sided alpha of 0.0125, with a total of 632 subjects, there was 89% power to show non-inferiority for investigator's assessment of clinical response at PTE in the mITT population. With an evaluability rate of 80%, there were 506 subjects provided 91% power to show non-inferiority in the CE population.

- **Blinding (masking)**

The investigator and sponsor were blinded to treatment arm assignments throughout the study. Both the iv and po phases of the study were double-blind and double-dummy.

- **Statistical methods**

Study populations

- The intent-to-treat (ITT) population consisted of all randomized subjects regardless of whether or not the subject received test article. A subject was considered randomized when the IxRS provided the test article assignment (ie, completes a randomization transaction).
- The mITT population consisted of all randomized subjects without a baseline sole Gram-negative ABSSSI pathogen.
- The micro-mITT population consisted of all subjects in the mITT population who had at least 1 Gram-positive causative bacterial pathogen identified at baseline.
- Two CE analysis sets were defined; the CE-EOT and the CE-PTE comprised mITT patients who received a minimum dose of study drug, had a qualifying ABSSSI, completed an outcome assessment, and met all other evaluability criteria detailed in the SAP. By definition, subjects with an indeterminate clinical outcome at the EOT or PTE visits were excluded from the relevant CE population.

Multiplicity

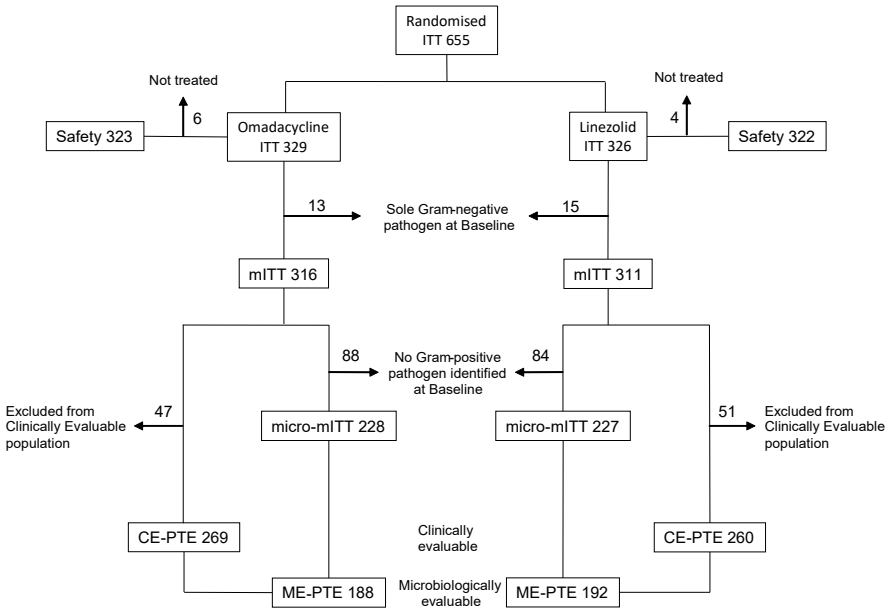
No adjustments were made. Confidence intervals for secondary outcomes were descriptive only.

Missing data

Subjects were defined as an indeterminate if the investigator could not determine whether the subject was a clinical success or failure at the EOT or PTE visits or the subject had a missing response. By definition, subjects with an indeterminate response were included in the denominator for analyses in the mITT and micro-mITT populations, and thus, were considered clinical failures. Subjects with an indeterminate response were excluded from the CE-EOT, CE-PTE, ME-EOT, and ME-PTE populations

Results (Study PTK0796-ABSI-1108)

Figure 4. Participant flow, Study PTK0796-ABSI-1108



CE = clinically evaluable, ITT = intent-to-treat, ME = microbiologically evaluable, mITT = modified intent-to-treat, micro-mITT = microbiological modified intent-to-treat, PTE = post therapy evaluation.
Source: applicant's Summary of Clinical Efficacy – ABSSSI.

Table 25. Subject Disposition, ITT population (Study PTK0796-ABSI-1108)

Parameter/ Category	Omadacycline (N = 329) n (%)	Linezolid (N = 326) n (%)	All Subjects (N = 655) n (%)	p-value[a]
Randomized	329 (100.0)	326 (100.0)	655 (100.0)	
Completed study treatment[b]	296 (90.0)	288 (88.3)	584 (89.2)	
Prematurely discontinued from study treatment	33 (10.0)	38 (11.7)	71 (10.8)	0.5314
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 subject	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[c]	7 (2.1)	6 (1.8)	13 (2.0)	
Completed study[d]	301 (91.5)	294 (90.2)	595 (90.8)	
Prematurely discontinued from study	28 (8.5)	32 (9.8)	60 (9.2)	0.5900
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 subject	9 (2.7)	4 (1.2)	13 (2.0)	
Physician decision	1 (0.3)	1 (0.3)	2 (0.3)	
Death[e]	1 (0.3)	2 (0.6)	3 (0.4)	
Other[c]	7 (2.1)	6 (1.8)	13 (2.0)	

AE = adverse event; ITT = intent-to-treat.

Source: Study PTK0796-ABSI-1108 CSR.

- **Conduct of the study**

Database lock: 09 June 2016

Data base unblind: 09 June 2016

The SAP was finalised on 24 May 2016, prior to unblinding, and the Applicant states that no knowledge about results was available when changing the alpha-level in the final SAP.

- **Baseline data**

Table 26. Demographics of Safety population (Study PTK0796-ABSI-1108)

Characteristics	Omadacycline (N = 323)	Linezolid (N = 322)	All Subjects (N = 645)	p-value
Gender, n (%)				
n	323	322	645	
Female	120 (37.2)	109 (33.9)	229 (35.5)	
Male	203 (62.8)	213 (66.1)	416 (64.5)	0.411
Race, n (%)				
n	323	322	645	
White	294 (91.0)	300 (93.2)	594 (92.1)	
Black or African American	16 (5.0)	8 (2.5)	24 (3.7)	
Asian	1 (0.3)	2 (0.6)	3 (0.5)	
American Indian or Alaska Native	7 (2.2)	5 (1.6)	12 (1.9)	
Native Hawaiian or Other Pacific Islander	1 (0.3)	3 (0.9)	4 (0.6)	
Other	4 (1.2)	4 (1.2)	8 (1.2)	0.506
Ethnicity, n (%)				
n	323	322	645	
Hispanic or Latino	84 (26.0)	91 (28.3)	175 (27.1)	
Not Hispanic or Latino	235 (72.8)	229 (71.1)	464 (71.9)	
Not reported/unknown	4 (1.2)	2 (0.6)	6 (0.9)	0.585
Age (years)				
n	323	322	645	
Mean (SD)	46.9 (15.45)	46.6 (15.30)	46.8 (15.36)	
Median	48.0	46.0	47.0	
Min, max	19, 88	18, 90	18, 90	0.810
Categorical age (years) n (%)				
n	323	322	645	
18-45	146 (45.2)	154 (47.8)	300 (46.5)	
> 45-65	141 (43.7)	136 (42.2)	277 (42.9)	
> 65	36 (11.1)	32 (9.9)	68 (10.5)	0.778
Height (cm)				
n	323	322	645	
Mean (SD)	171.41 (9.201)	171.34 (9.546)	171.38 (9.368)	
Median	172.70	171.75	172.00	
Min, max	148.0, 200.6	146.0, 195.0	146.0, 200.6	0.994
Weight (kg)				
n	323	321	644	
Mean (SD)	82.26 (19.685)	82.76 (19.969)	82.51 (19.813)	
Median	79.70	79.00	79.25	
Min, max	45.0, 147.4	45.5, 151.0	45.0, 151.0	0.775
BMI (kg/m^2)				
n	323	321	644	
Mean (SD)	27.98 (6.330)	28.14 (6.233)	28.06 (6.278)	
Median	26.99	26.62	26.86	
Min, max	16.9, 53.6	16.2, 54.7	16.2, 54.7	0.745
CrCL (local lab) n (%)				
n	323	321	644	
Normal renal function (> 80 mL/min)	277 (85.8)	276 (86.0)	553 (85.9)	
Mild renal impairment (> 50-80 mL/min)	32 (9.9)	35 (10.9)	67 (10.4)	
Moderate renal impairment (30-50 mL/min)	12 (3.7)	9 (2.8)	21 (3.3)	
Severe renal impairment (< 30 mL/min)	2 (0.6)	1 (0.3)	3 (0.5)	0.818

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

Source: Study PTK0796-ABSI-1108 CSR Table 10.

Table 27. Medical history occurring in >10% of Safety population (Study PTK0796-ABSI-1108)

Characteristics	Omadacycline (N = 323) n (%)	Linezolid (N = 322) n (%)
Subjects with at least 1 medical history event	269 (83.3)	275 (85.4)
Drug abuse	174 (53.9)	169 (52.5)
Tobacco user	131 (40.6)	127 (39.4)
Hepatitis C[a]	94 (29.1)	90 (28.0)
Hypertension	66 (20.4)	81 (25.2)
Anxiety	63 (19.5)	69 (21.4)
Depression	50 (15.5)	49 (15.2)
Headache	44 (13.6)	41 (12.7)
Drug hypersensitivity[b]	34 (10.5)	35 (10.9)
Insomnia	34 (10.5)	30 (9.3)
Diabetes mellitus[c]	24 (7.4)	35 (10.9)

Source: Study PTK0796-ABSI-1108 CSR Table 11.

- **Causative organisms**

The frequency of specific species amongst pooled ABSSSI Phase 3 study data is presented in Section 3.3.6. Analysis performed across trials (pooled analyses). Only 11 subjects in the omadacycline arm and 9 subjects in the linezolid arm had positive blood cultures (<5% of mITT population).

- **Numbers analysed**

Table 28. Analysis populations Overall and by Geographic Region (Study PTK0796-ABSI-1108)

Region	Population	Omadacycline		Linezolid		All Subjects	
		n	(%)	n	(%)	n	(%)
Overall	**ITT**	**329**		**326**		**655**	
	Safety	323	(98.2)	322	(98.8)	645	(98.5)
	mITT	316	(96.0)	311	(95.4)	627	(95.7)
	micro-mITT	228	(69.3)	227	(69.6)	455	(69.5)
	CE-EOT	278	(84.5)	273	(83.7)	551	(84.1)
	CE-PTE	269	(81.8)	260	(79.8)	529	(80.8)
	ME-EOT	195	(59.3)	198	(60.7)	393	(60.0)
	ME-PTE	188	(57.1)	192	(58.9)	380	(58.0)
North America (USA)	**ITT**	**208**		**207**		**415**	
	Safety	202	(97.1)	203	(98.1)	405	(97.6)
	mITT	207	(99.5)	202	(97.6)	409	(98.6)
	micro-mITT	173	(83.2)	166	(80.2)	339	(81.7)
	CE-EOT	171	(82.2)	168	(81.2)	339	(81.7)
	CE-PTE	166	(79.8)	161	(77.8)	327	(78.8)
	ME-EOT	141	(67.8)	139	(67.1)	280	(67.5)
	ME-PTE	136	(65.4)	136	(65.7)	272	(65.5)
Eastern Europe	**ITT**	**92**		**92**		**184**	
	Safety	92	(1 000)	92	(1 000)	184	(1 000)
	mITT	81	(88.0)	84	(91.3)	165	(89.7)
	micro-mITT	48	(52.2)	56	(60.9)	104	(56.5)
	CE-EOT	81	(88.0)	82	(89.1)	163	(88.6)
	CE-PTE	78	(84.8)	77	(83.7)	155	(84.2)
	ME-EOT	48	(52.2)	54	(58.7)	102	(55.4)
	ME-PTE	46	(50.0)	52	(56.5)	98	(53.3)
Western Europe	**ITT**	**24**		**23**		**47**	
	Safety	24	(100.0)	23	(100.0)	47	(100.0)
	mITT	23	(95.8)	21	(91.3)	44	(93.6)
	micro-mITT	7	(29.2)	4	(17.4)	11	(23.4)

	CE-EOT	21	(87.5)	19	(82.6)	40	(85.1)
	CE-PTE	20	(83.3)	18	(78.3)	38	(80.9)
	ME-EOT	6	(25.0)	4	(17.4)	10	(21.3)
	ME-PTE	6	(25.0)	3	(13.0)	9	(19.1)
Latin America	**ITT**	**5**		**4**		**9**	
	Safety	5	(100.0)	4	(100.0)	9	(100.0)
	mITT	5	(100.0)	4	(100.0)	9	(100.0)
	micro-mITT	0		1	(25.0)	1	(11.1)
	CE-EOT	5	(100.0)	4	(100.0)	9	(100.0)
	CE-PTE	5	(100.0)	4	(100.0)	9	(100.0)
	ME-EOT	0		1	(25.0)	1	(11.1)
	ME-PTE	0		1	(25.0)	1	(11.1)

Table compiled by assessor. Source data: Study PTK0796-ABSI-1108 CSR Table 14.1.1.2.

- **Outcomes and estimation**

Primary efficacy analysis

Table 29. Efficacy: Overall Clinical Response at PTE in mITT, and CE-PTE Populations (Study PTK0796-ABSI-1108)

Efficacy Outcome	Omadacycline n (%)	Linezolid n (%)	Difference (95% CI)
mITT	**N = 316**	**N = 311**	
Clinical success	272 (86.1)	260 (83.6)	2.5 (-3.2, 8.1)
Clinical failure or indeterminate	44 (13.9)	51 (16.4)	
Clinical failure	20 (6.3)	27 (8.7)	
Discontinued test article with a need for rescue antibacterial therapy	10 (3.2)	10 (3.2)	
Potentially effective antibacterial received for different indication	6 (1.9)	5 (1.6)	
Clinical failure at EOT	15 (4.7)	18 (5.8)	
Discontinued test article with a need for rescue antibacterial therapy	12 (3.8)	8 (2.6)	
AE requiring discontinuation of test article	12 (3.8	8 (2.6)	
Unplanned major surgical intervention	0	1 (0.3)	
Indeterminate	24 (7.6)	24 (7.7)	
CE-PTE	**N = 269**	**N = 260**	
Clinical success	259 (96.3)	243 (93.5)	2.8 (-0.9, 7.1)
Clinical failure	10 (3.7)	17 (6.5)	

CI = confidence interval, CE = clinically evaluable, CSR = clinical study report, EOT = end of treatment, EMA = European Medicines Agency, mITT = modified intent-to-treat, PTE = post therapy evaluation.
Source adapted from: Study PTK0796-ABSI-1108 EMA CSR Table 2 and Table 14.2.2.2.

Given that the lower limit of the 95% CI for the treatment difference between arms in the mITT and CE populations was above the pre-specified margin of -10%, omadacycline was considered non-inferior to linezolid. Sensitivity analysis of the primary outcome conducted by constructing an unstratified 95% CI yielded results almost identical to the primary analysis in both mITT and CE populations.

Sensitivity analysis of the co-primary efficacy endpoints in the all-treated population (all randomised subjects receiving at least 1 dose of test article) was provided as recommended in CHMP Scientific Advice. In the Safety population, clinical success rates were high (87.3% for omadacycline, 85.4% for linezolid) and comparable between both treatment groups (difference [95% CI]: 1.9 [-3.5, 7.2]. The 95% CI for the sensitivity analysis without stratification was [-3.4, 7.3].

When patients with indeterminate response were imputed with clinical success, sensitivity analysis produced similar results to the primary analysis.

Secondary efficacy analyses

Microbiological response (per-subject)

Nearly all cases of microbiological eradication were "presumed" (i.e. there were very few post-baseline cultures performed) in the micro-mITT.

Table 30. Microbiological Response at EOT and overall microbiological response at PTE in micro-mITT, ME-EOT, and ME-PTE Populations (Study PTK0796-ABSI-1108)

Visit/Outcome	Omadacycline n (%)	Linezolid n (%)	Difference (95% CI)
micro-mITT	N = 228	N = 227	
Microbiological response at EOT visit			
Favourable	202 (88.6)	199 (87.7)	0.9 (-5.1, 7.0)
Eradication	0	4 (1.8)	-
Presumed eradication	202 (88.6)	195 (85.9)	-
Unfavourable	7 (3.1)	13 (5.7)	-
Persistence	1 (0.4)	2 (0.9)	-
Presumed persistence	6 (2.6)	11 (4.8)	-
Indeterminate	19 (8.3)	15 (6.6)	-
Overall microbiological response at PTE visit			
Favourable	194 (85.1)	189 (83.3)	1.8 (-5.0, 8.6)
Unfavourable	11 (4.8)	19 (8.4)	-
Indeterminate	23 (10.1)	19 (8.4)	-
ME-EOT	N = 195	N = 198	
Microbiological response at EOT visit			
Favourable	192 (98.5)	191 (96.5)	2.0 (-1.3, 5.9)
Eradication	0	2 (1.0)	-
Presumed eradication	192 (98.5)	189 (95.5)	-
Unfavourable	3 (1.5)	7 (3.5)	-
Persistence	1 (0.5)	1 (0.5)	-
Presumed persistence	2 (1.0)	6 (3.0)	-
ME-PTE	N = 188	N = 192	
Microbiological response at PTE Visit			
Favourable	184 (97.9)	180 (93.8)	4.1 (0.1, 8.7)
Eradication	1 (0.5)	2 (1.0)	-
Presumed eradication	183 (97.3)	178 (92.7)	-
Unfavourable	4 (2.1)	12 (6.3)	-
Presumed persistence	4 (2.1)	12 (6.3)	-
Overall microbiological response at PTE visit			
Favourable	184 (97.9)	180 (93.8)	4.1 (0.1, 8.7)
Unfavourable	4 (2.1)	12 (6.3)	-

CI = confidence interval, CSR = clinical study report, EMA = European Medicines Agency, EOT = end of treatment; ME = microbiologically evaluable; micro-mITT = microbiological modified intent-to-treat; PTE = post therapy evaluation.
Source: Study PTK0796-ABSI-1108 CSR, Table 6.

Microbiological response (per-pathogen)

Similar rates of overall favourable microbiological response were observed for both treatment arms for *S. aureus* and pooled non-*S. aureus* species:

Table 31. Overall microbiological response at PTE, according to pathogen, micro-mITT and population (Study PTK0796-ABSI-1108)

Pathogen	Favourable overall microbiological response at PTE n/N (%)	
	Omadacycline (n=228)	Linezolid (n=227)
Staphylococcus aureus	130/156 (83)	126/151 (83)
MSSA	74/88 (84)	84/102 (82)
MRSA	57/69 (83)	43/50 (86)
Non-*S. aureus* organisms	148/177 (84)	133/169 (79)

Table compiled by assessor. Source data: Study PTK0796-ABSI-1108 CSR v2 Table 14.2.13.1.1.

Additional efficacy analyses

Mono- and poly-microbial infections

Table 32. Overall clinical success and overall favourable microbiological response at PTE, micro-mITT population, according to infection type (Study PTK0796-ABSI-1108)

Infection type	Overall clinical success at PTE n/N (%)			Overall favourable microbiological response at PTE n/N (%)	
	Omadacycline (228)	Linezolid (227)	Difference (95% CI)	Omadacycline (228)	Linezolid (227)
Mono-microbial G+	137/156 (88)	145/171 (85)	3.0 (-4.6, 10.6)	137/156 (88)	145/171 (85)
Poly-microbial G+	23/31 (74)	22/27 (82)	-7.3 (-28.5, 15.1)	24/31 (77)	22/27 (82)
Poly-microbial mixed	33/41 (81)	22/29 (76)	4.6 (-14.7, 25.5)	33/41 (81)	22/29 (76)

Table complied by assessor. Source data: Study PTK0796-ABSI-1108 CSR Tables 14.2.2.4.1 and 14.2.12.4.1.

Clinical outcome according to baseline pathogen and/or MIC

Pooled clinical response results according to pathogen and baseline MIC are discussed below in Section 3.3.6. Analysis performed across trials (pooled analyses).

New and super-infections

Table 33. New and super-infections (Study PTK0796-ABSI-1108)

Subject	Treatment	New or super-infection
262-0094 38M	6d iv linezolid	*Clostridium sordellii* (Day 3), super-infection
262-0011 42F	5d iv 6d po omadacycline	*Streptococcus intermedius* (Day 22), new infection
201-0001 59F	10d iv linezolid	*P. aeruginosa* and *K. pneumoniae* (Day 10), new infection
254-0003 61M	4d iv 7d po linezolid	MSSA (Day 17), new infection

Table compiled by assessor. Source data: Study PTK0796-ABSI-1108 EMA CSR.

Concordance of clinical outcome across visits

At both of the later evaluation visits, the omadacycline arm demonstrated numerically better continuity of cure than linezolid, with 4/268 ECR successes deemed failures at EOT and 7/268 deemed failures at PTE in the omadacycline arm, vs 9/266 ECR successes deemed failures at EOT and 16/266 deemed failures at PTE in the linezolid arm. The number of ECR successes later deemed indeterminate (including subjects not clinically evaluable) was the same in both treatment arms.

Sub-group analyses

Most subjects in the mITT population had comparable clinical success by type of infection (wound infection, cellulitis/erysipelas, and major abscess, ~80%, 85-91% and ~85%, respectively). Perhaps unsurprisingly, the highest clinical success rates (~88%) were observed in subjects with smallest lesion size (≤300 cm^2) and the lowest (72-82%) in subjects with the greatest lesion size (≥1000 cm^2). There were no obvious differences revealed by sub-group analysis according to geographic region, EU vs non-EU, history of IV drug use, bacteraemia or SIRS. Some numerical differences are noted, but small absolute numbers in some of these groups precludes any robust conclusions. Sub-group analysis was also provided for subjects who switched to PO treatment vs subjects who did not switch. For subjects in mITT population who did not switch to po treatment, omadacycline was inferior to linezolid as lower limit of 97.5% confidence interval was lower than -10% (-13.4%). However, this was a small sub-group (14 omadacycline, 15 linezolid) and only and exploratory analysis.

3.3.5.2.2. Study PTK0796-ABSI-16301 - *A Phase 3 Randomised, Double-Blind, Multi-Centre Study to Compare the Safety and Efficacy of Oral Omadacycline to Oral Linezolid (Zyvox®) for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)*

Methods (Study PTK0796-ABSI-16301)

- **Study participants**

Subjects 18 to 80 years of age from 53 US centres. Inclusion criteria were as for Study PTK0896-ABSI-1108. Subjects who received only a single dose of short-acting (standard dosing regimen >once a day), non-oxazolidinone antibiotic were eligible for enrolment (capped at 25%).

- **Treatments**

Subjects were randomised (1:1) to one of the following two treatments, for a total of 7 to 14 days:

  - Omadacycline, 450 mg po q24h for 2 doses, followed by 300 mg po q24h.
  - Linezolid, 600 mg po q12h.

Subjects could receive adjunctive Gram-negative cover at the discretion of the investigator if a Gram-negative pathogen, anaerobe or linezolid-resistant pathogen was detected at baseline.

- **Objectives**

Primary objective: to demonstrate that omadacycline administered po for 7 to 14 days was non-inferior to linezolid administered po for 7 to 14 days in the treatment of adult subjects with ABSSSI known or suspected to be due to Gram-positive pathogens.

Secondary objectives: as for study PTK0796-ABSI-1108.

- **Outcomes/endpoints -** As for study PTK0796-ABSI-1108.

- **Sample size**

Assuming an 85% outcome rate in both treatment groups, a non-inferiority margin of 10%, and a 1-sided alpha of 0.025, with a total of 704 subjects, there was more than 90% power to show non-inferiority for IACR at PTE in the mITT population. With an evaluability rate of 80%, there were 564 subjects in the CE population. Assuming a 90% outcome rate in both treatment groups, a non-inferiority margin of 10%, and a 1-sided alpha of 0.025, 564 subjects provided more than 90% power to show non-inferiority in the CE population.

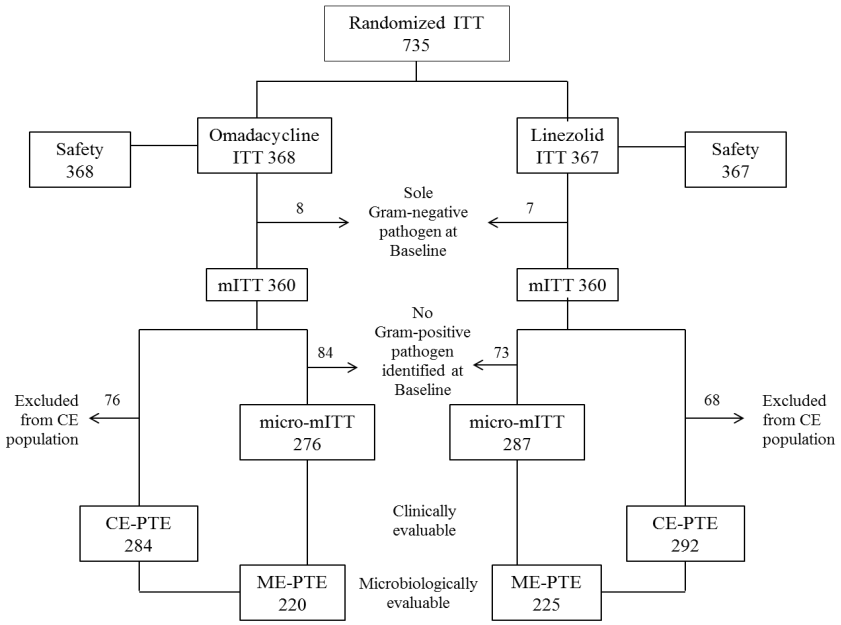
- **Blinding (masking)**

Investigator and sponsor were blinded to treatment allocation. Double-dummy was used throughout.

- **Statistical methods -** As for study PTK0796-ABSI-1108.

Results (Study PTK0796-ABSI-16301)

Figure 5. Participant flow, Study PTK0796-ABSI-16301



CE = clinically evaluable, ITT = intent-to-treat, ME = microbiologically evaluable, mITT = modified intent-to-treat, micro-mITT = microbiological modified intent-to-treat, PTE = post therapy evaluation.
Source: applicant's Summary of Clinical Efficacy – ABSSSI.

Table 34. Subject disposition, ITT population (Study PTK0796-ABSI-16301)

Parameter/ Category	Omadacycline (N = 368) n (%)	Linezolid (N = 367) n (%)	All Subjects (N = 735) n (%)	p-value[a]
Randomized	368 (100.0)	367 (100.0)	735 (100.0)	
Completed study treatment[b]	328 (89.1)	315 (85.8)	643 (87.5)	
Prematurely discontinued from study treatment	40 (10.9)	52 (14.2)	92 (12.5)	0.1829
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 subject	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[c]	314 (85.3)	310 (84.5)	624 (84.9)	
Prematurely discontinued from study	54 (14.7)	57 (15.5)	111 (15.1)	0.7583
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 subject	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)	

AE = adverse event; EOT = end of treatment; ITT = intent-to-treat; PTE = post therapy evaluation.

Source: Study PTK0796-ABSI-16301 CSR Table 4.

- **Conduct of the study**

Database lock: 30 June 2017

Database unblind: 03 July 2017

- **Baseline data**

Table 35. Demographics of Safety population (Study PTK0796-ABSI-1108)

Characteristics	Omadacycline (N = 368)	Linezolid (N = 367)	All Subjects (N = 735)	p-value
Gender, n (%)				
n	368	367	735	
Female	126 (34.2)	147 (40.1)	273 (37.1)	
Male	242 (65.8)	220 (59.9)	462 (62.9)	0.109
Race, n (%)				
n	368	367	735	
White	327 (88.9)	341 (92.9)	668 (90.9)	
Black or African American	22 (6.0)	13 (3.5)	35 (4.8)	
Asian	3 (0.8)	5 (1.4)	8 (1.1)	
American Indian or Alaska Native	7 (1.9)	3 (0.8)	10 (1.4)	
Native Hawaiian or Other Pacific Islander	3 (0.8)	0	3 (0.4)	
Other	6 (1.6)	5 (1.4)	11 (1.5)	0.176
Ethnicity, n (%)				
n	368	367	735	
Hispanic or Latino	154 (41.8)	156 (42.5)	310 (42.2)	
Not Hispanic or Latino	214 (58.2)	211 (57.5)	425 (57.8)	
Not reported/unknown	0	0	0	0.881
Age (years)				
n	368	367	735	
Mean (SD)	42.8 (12.72)	44.5 (13.11)	43.7 (12.94)	
Median	41.0	46.0	43.0	
Min, Max	18, 86	20, 84	18, 86	0.109
Categorical age (years) n (%)				
n	368	367	735	
18-45	213 (57.9)	183 (49.9)	396 (53.9)	
> 45-65	141 (38.3)	164 (44.7)	305 (41.5)	
> 65-75	11 (3.0)	12 (3.3)	23 (3.1)	0.131
> 75	3 (0.8)	8 (2.2)	11 (1.5)	
Height (cm)				
n	368	367	735	
Mean (SD)	171.33 (10.020)	169.45 (9.745)	170.39 (9.922)	
Median	171.00	170.00	170.20	
Min, max	137.0, 196.9	132.1, 193.0	132.1, 196.9	0.018
Weight (kg)				
n	368	367	735	
Mean (SD)	81.62 (18.286)	80.15 (19.778)	80.89 (19.047)	
Median	79.40	76.20	77.70	
Min, max	41.7, 167.0	44.5, 156.3	41.7, 167.0	0.074
BMI (kg/m^2)				
n	368	367	735	
Mean (SD)	27.91 (6.472)	27.93 (6.556)	27.92 (6.510)	
Median	26.71	26.54	26.64	
Min, max	16.3, 71.3	16.7, 54.1	16.3, 71.3	0.911
Renal function (central lab) n (%)				
n	365	363	728	
Normal renal function (CrCL > 80 mL/min)	343 (94.0)	340 (93.7)	683 (93.8)	
Mild renal impairment (CrCL > 50-80 mL/min)	21 (5.8)	17 (4.7)	38 (5.2)	
Moderate renal impairment (CrCL 30-50 mL/min)	1 (0.3)	6 (1.7)	7 (1.0)	
Severe renal impairment (CrCL < 30 mL/min)	0	0	0	0.156

Source: Study PTK0796-ABSI-16301 CSR Table 7.

Table 36. Medical history occurring in >10% of Safety population (Study PTK0796-ABSI-16301)

Characteristics	Omadacycline (N = 368) n (%)	Linezolid (N = 367) n (%)
Subjects with at least 1 medical history event	349 (94.8)	356 (97.0)
Drug abuse	268 (72.8)	258 (70.3)
Tobacco user	147 (39.9)	146 (39.8)
Hepatitis C	116 (31.5)	129 (35.1)
Anxiety	76 (20.7)	78 (21.3)
Depression	69 (18.8)	62 (16.9)
Subcutaneous abscess	68 (18.5)	66 (18.0)
Wound infection	59 (16.0)	70 (19.1)
Hypertension	58 (15.8)	59 (16.1)
Skin bacterial infection	52 (14.1)	59 (16.1)
Back pain	48 (13.0)	47 (12.8)
Insomnia	48 (13.0)	36 (9.8)
Drug hypersensitivity	45 (12.2)	42 (11.4)
Myopia	44 (12.0)	41(11.2)
Tobacco abuse	44 (12.0)	41 (11.2)
Headache	36 (9.8)	42 (11.4)

Coding of PT based on MedDRA Version 17.1.
Percentages were based on the number of subjects in the Safety population.
Preferred terms were sorted by decreasing frequency within the omadacycline column.
ABSSSI = acute bacterial skin and skin structure infection; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

Source: Study PTK0796-ABSI-16301 CSR Table 8.

- **Causative organisms**

The frequency of specific species across pooled Phase 3 study data is presented in Section 3.3.6. Analysis performed across trials (pooled analyses). Only 2 subjects in the omadacycline arm and 8 subjects in the linezolid arm had positive blood cultures (<2% of mITT population).

- Numbers analysed

Table 37. Analysis populations (Study PTK0796-ABSI-16301)

Region	Population	Omadacycline		Linezolid		All Subjects	
		n	(%)	n	(%)	n	(%)
Overall	**ITT**	**368**		**367**		**735**	
	Safety	368	(100)	367	(100)	735	(100)
	mITT	360	(97.8)	360	(98.1)	720	(98.0)
	micro-mITT	276	(75.0)	287	(78.2)	563	(76.6)
	CE-EOT	304	(82.6)	296	(80.7)	600	(81.6)
	CE-PTE	284	(77.2)	292	(79.6)	576	(78.4)
	ME-EOT	233	(63.3)	229	(62.4)	462	(62.9)
	ME-PTE	220	(59.8)	225	(61.3)	445	(60.5)

Source: adapted from Study PTK0796-ABSI-16301 CSR Table 6.

- **Outcomes and estimation**

Primary efficacy analysis

Table 38. Efficacy: Overall Clinical Response at PTE in mITT, and CE-PTE Populations (Study PTK0796-ABSI-16301)

Efficacy Outcome	Omadacycline n (%)	Linezolid n (%)	Difference (95% CI)
mITT	**N = 360**	**N = 360**	
Clinical success	303 (84.2)	291 (80.8)	3.3 (-2.2, 9.0)
Clinical failure or indeterminate	57 (15.8)	69 (19.2)	
Clinical failure	12 (3.3)	21 (5.8)	
Infection required alternative antibacterial	1 (0.3)	1 (0.3)	
Other (non-compliance)	0	1 (0.3)	
Clinical failure at EOT	11 (3.1)	19 (5.3)	
Discontinued test article with a need for rescue antibacterial therapy	5 (1.4)	11 (3.1)	
Potentially effective antibacterial received for different indication	1 (0.3)	0	
AE requiring discontinuation of test article	3 (0.8)	4 (1.1)	
Other	3 (0.8)	6 (1.7)	
Indeterminate	45 (12.5)	48 (13.3)	
CE-PTE	**N = 284**	**N = 292**	
Clinical success	278 (97.9)	279 (95.5)	2.3 (-0.5, 5.8)
Clinical failure	6 (2.1)	13 (4.5)	

CI = confidence interval, CE = clinically evaluable, CSR = clinical study report, EOT = end of treatment, EMA = European Medicines Agency, mITT = modified intent-to-treat, PTE = post therapy evaluation.
Source: adapted from Study PTK0796-ABSI-16301 EMA CSR Table 3 and Table 14.2.2.2.

Given that the lower limit of the 95% CI for the treatment difference between arms in the mITT and CE populations was above the pre-specified margin of -10%, omadacycline was considered non-inferior to linezolid. Sensitivity analysis of the primary outcome conducted by constructing an unstratified 95% CI yielded results almost identical to the primary analysis in both mITT and CE populations.

Sensitivity analysis of the co-primary efficacy endpoints in the all-treated population (all randomised subjects receiving at least 1 dose of test article) was provided as recommended in CHMP Scientific Advice. In the Safety population, clinical success rates were high (84.2% for omadacycline, 80.7% for linezolid) and comparable between both treatment groups (difference [95% CI]: 3.6 [-1.9, 9.1] for the analysis with and without stratification).

When patients with indeterminate response were imputed with clinical success, sensitivity analysis produced similar results to the primary analysis.

Secondary efficacy analyses

Microbiological response (per-subject)

Table 39. Microbiological Response at EOT and PTE in micro-mITT, ME-EOT, and ME-PTE Populations (Study PTK0796-ABSI-16301)

Visit/Outcome	Omadacycline n (%)	Linezolid n (%)	Difference (95% CI)
micro-mITT	N = 276	N = 287	
Microbiological response at EOT visit			
Favorable	246 (89.1)	238 (82.9)	6.2 (0.4, 12.0)
Eradication	1 (0.4)	2 (0.7)	-
Presumed eradication	245 (88.8)	236 (82.2)	-
Unfavorable	10 (3.6)	15 (5.2)	-
Persistence	4 (1.4)	6 (2.1)	-
Presumed persistence	6 (2.2)	9 (3.1)	-
Indeterminate	20 (7.2)	34 (11.8)	-
Overall microbiological response at PTE visit			
Favorable	229 (83.0)	224 (78.0)	4.9 (-1.5, 11.6)
Unfavorable	11 (4.0)	19 (6.6)	-
Indeterminate	36 (13.0)	44 (15.3)	-
ME-EOT	N = 233	N = 229	
Microbiological response at EOT visit			
Favorable	229 (98.3)	224 (97.8)	0.5 (-2.4, 3.6)
Eradication	1 (0.4)	2 (0.9)	-
Presumed eradication	228 (97.9)	222 (96.9)	-
Unfavorable	4 (1.7)	5 (2.2)	-
Persistence	3 (1.3)	1 (0.4)	-
Presumed persistence	1 (0.4)	4 (1.7)	-
ME-PTE	N = 220	N = 225	
Microbiological response at PTE visit			
Favorable	215 (97.7)	215 (95.6)	2.2 (-1.2, 6.2)
Presumed eradication	215 (97.7)	215 (95.6)	-
Unfavorable	5 (2.3)	10 (4.4)	-
Persistence	1 (0.5)	1 (0.4)	-
Presumed persistence	4 (1.8)	9 (4.0)	-
Overall microbiological response at PTE visit			
Favorable	215 (97.7)	214 (95.1)	2.6 (-0.8, 6.7)
Unfavorable	5 (2.3)	11 (4.9)	-

CI = confidence interval, CSR = clinical study report, EOT = end of treatment, ME = microbiologically evaluable, micro-mITT = microbiological modified intent-to-treat, PTE = post therapy evaluation.
Source: Study PTK0796-ABSI-16301 EMA CSR Table 6.

Nearly all cases of microbiological eradication were "presumed" (i.e. there were very few post-baseline cultures performed) in the micro-mITT.

Microbiological response (per-pathogen)

Better rates of overall favourable microbiological response were observed for omadacycline for *S. aureus* and pooled non-*S. aureus* species:

Table 40. Overall microbiological response at PTE, according to pathogen, micro-mITT and population (Study PTK0796-ABSI-16301)

Pathogen	Favourable overall microbiological response at PTE n/N (%)	
	Omadacycline (n=276)	Linezolid (n=287)
Staphylococcus aureus	182/220 (83)	187/233 (80)
MSSA	97/120 (81)	104/130 (80)
MRSA	89/104 (86)	85/107 (79)
Non-*S. aureus* organisms	199/238 (84)	145/197 (74)

Table compiled by assessor. Source data: Study PTK0796-ABSI-16301 CSR Table 14.2.13.1.1.

Additional efficacy analyses

Mono- and poly-microbial infections

Table 41. Overall clinical success and overall favourable microbiological response at PTE in the micro-mITT population according to type of infection (Study PTK0796-ABSI-16301)

Infection type	Overall clinical success at PTE n/N (%)			Favourable microbiological response n/N (%)	
	Omadacycline (276)	Linezolid (287)	Difference (95% CI)	Omadacycline (276)	Linezolid (276)
Mono-microbial G+	155/184 (84)	167/212 (79)	5.5 (-2.3, 13.1)	155/184 (84)	167/212 (79)
Poly-microbial G+	49/60 (82)	26/37 (70)	11.4 (-5.6, 29.7)	49/60 (82)	26/37 (70)
Poly-microbial mixed	25/32 (78)	31/38 (82)	-3.5 (-23.3, 15.6)	25/32 (78)	31/38 (82)

Table complied by assessor. Source data: Study PTK0796-ABSI-16301 CSR Tables 14.2.2.4.1 and 14.2.12.4.1.

Clinical outcome according to baseline pathogen and/or MIC

Pooled clinical response results according to pathogen and baseline MIC are discussed below in Section 3.3.6. Analysis performed across trials (pooled analyses).

New and super-infections

Table 42. New and super-infections (Study PTK0796-ABSI-16301)

Subject	Treatment	New or super-infection
608-3031 34M	3d omadacycline	MSSA (Day 2), super-infection
610-3046 52M	10d omadacycline	- *E. coli* (Day 7), super-infection - *Bacteroides thetaiotaomicron*, *Citrobacter freundii* and *Morganella morganii* (Day 11), new infection - *Citrobacter braakii* and *Anaerococcus tetradius* (Day 18), new infections
608-3138 51M	3d linezolid	*Proteus mirabilis* (Day 3), new infection
610-3002 48M	3d linezolid	*Staphylococcus aureus* (Day 6), new infection
636-3013 48M	17d linezolid	*Klebsiella pneumoniae* and *Stenotrophomonas maltophilia* (Day 18), new infections

Table compiled by assessor. Source data: Study PTK0796-ABSI-16301 EMA CSR.

Concordance of clinical outcome across visits

At both of the later evaluation visits, the omadacycline arm demonstrated numerically better continuity of cure than linezolid, with 3/315 ECR successes deemed failures at EOT and 4/315 deemed failures at PTE in the omadacycline arm, vs 8/297 ECR successes deemed failures at EOT and 10/297 deemed failures at PTE in the linezolid arm.

Sub-group analyses

Most subjects in the mITT population had comparable clinical success by type of infection (wound infection, cellulitis/erysipelas, and major abscess, 77-82%, 88-93% and 79-84%, respectively). Perhaps unsurprisingly, the highest clinical success rates (~88%) were observed in subjects with smallest lesion size (≤300 cm^2) and the lowest (~75%) in subjects with the greatest lesion size (≥1000 cm^2). There were no obvious differences revealed by sub-group analysis according to

geographic region, EU vs non-EU, history of IV drug use, bacteraemia or SIRS. Some numerical differences are noted, but small absolute numbers in these groups precludes robust conclusions.

3.3.5.2.3. Study PTK0796-CABP-1200 - *A Phase 3 Randomised, Double-Blind, Multi-Centre, Non-inferiority Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Moxifloxacin IV/PO for Treating Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)*

Methods (Study PTK0796-CABP-1200)

- **Study participants**

Male and female subjects aged 18 years or older, enrolled across 86 global sites with CABP, fulfilling all of the below criteria and expected to require at least 3 days' iv treatment:

1. Had at least 3 of the following symptoms:
   - Cough
   - Production of purulent sputum
   - Dyspnoea
   - Pleuritic chest pain
2. Had at least 2 of the following abnormal vital signs:
   - Fever or hypothermia documented by the investigator (temperature > 38.0°C [100.4°F] or < 36.0°C [95.5°F])
   - Hypotension with systolic blood pressure (SBP) less than 90 mm Hg
   - Heart rate (HR) greater than 90 beats per min (bpm)
   - Respiratory rate (RR) greater than 20 breaths/min
3. Had at least 1 clinical sign or laboratory finding associated with CABP:
   - Hypoxemia (partial pressure of arterial oxygen [PaO2] < 60 mm Hg by arterial blood gas [ABG] or oxygen saturation < 90% by pulse oximetry)
   - Physical examination findings of pulmonary consolidation (eg, dullness on percussion, bronchial breath sounds, or egophony)
   - An elevated total white blood cell (WBC) count (> 12,000 cells/mm3) or leukopenia (WBC < 4,000 cells/mm3) or elevated immature neutrophils (> 15% band forms regardless of total peripheral WBC count)
4. Radiographically-confirmed pneumonia, ie, new or progressive pulmonary infiltrate(s) on chest X-ray or chest computed tomography (CT) scan consistent with acute bacterial pneumonia within 24 h prior to the first dose of test article.
5. Had disease categorised as being Pneumonia Outcomes Research Team (PORT) Risk Class II, III, or IV at Screening.

Principal exclusion criteria:

(a) having received 1 or more dose of potentially effective systemic antibiotic in the 72 h prior to the first dose of test article (unless infecting organism shown to be intermediate or resistant to initial treatment, or only a single dose of short-acting antibiotic (dosed more than once daily) was received (capped at 25%)),

(b) suspected or known to have CABP caused by a pathogen resistant to either test article (eg, *K. pneumoniae*, *Pseudomonas aeruginosa*, *Pneumocystis jiroveci*, obligate anaerobes, mycobacteria, fungal pathogens),

(c) suspected or confirmed empyema, lung abscess, hospital-acquired pneumoniae (HAP) (defined as onset of clinical signs or symptoms ≥48 h after hospitalisation) or healthcare associated

pneumonia (HCAP) (defined as pneumonia acquired in long-term or intermediate healthcare facility or presenting following a recent hospitalisation, as specified in the protocol),

(d) requiring acute intervention to stabilise blood pressure/ tissue perfusion, or having evidence of septic shock (defined by all of fever >38 degrees Celsius, hypothermia <36 degrees Celsius, tachycardia >90 bpm, tachypnoea > 20 bpm, deranged WBC count, systolic hypotension <90 mmHg despite fluid challenge, perfusion abnormalities including lactic acidosis, oliguria, change in mental status),

(e) haemodynamically unstable despite fluid resuscitation, or requiring pressor agents

(f) known or suspected neoplastic lung disease, aspiration, cystic fibrosis, active tuberculosis, bronchiectasis, bronchial obstruction, chronic neurological disorder affecting airway clearance, chronic obstructive pulmonary disease (COPD).

(g) pre-existing hepatic, renal, immunological or cardiac disease as defined in the protocol

Subject randomization was stratified by PORT Risk Class (II or III/IV), receipt of an allowed prior antibacterial therapy in the 72 hours prior to study treatment, and geographic region. The number of subjects in PORT Risk Class II was limited to 15% of randomized subjects and subjects with allowed prior antibacterial therapy limited to 25%.

- **Treatments**

Subjects were randomised (1:1) to 1 of the following 2 treatment arms, to receive at least 3 days iv treatment, and between 7 and at most 14 days total treatment:

- Omadacycline, 100 mg iv q12h (first 2 doses), followed by 100 mg iv q24h, followed by optional switch to 300 mg po q24h after at least 3 days of iv treatment.
- Moxifloxacin, 400 mg iv q24h, followed by optional switch to 400 mg po q24h after at least 3 days of iv treatment.

- **Objectives**

Primary objective: to demonstrate that omadacycline 100 mg iv q12h for 2 doses, followed by 100 mg iv/300 mg po q24h, was non-inferior to moxifloxacin 400 mg iv/po q24h in the treatment of adults with CABP.

Secondary objectives:

- to evaluate the safety of omadacycline in adults subjects with CABP.
- to evaluate the clinical response according to the causative pathogen.
- to characterise the PK of omadacycline in adults subjects with CABP.

- **Outcomes/endpoints**

Structured evaluations were conducted at Early Clinical Response (48-72 h after first dose), End of Treatment (EOT, within 2 d of last dose), and Post Therapy Evaluation (PTE, 5-10 d after last dose).

Co-primary efficacy endpoint: overall assessment of clinical response at PTE (derived from IACR at EOT and PTE) in the ITT and CE-PTE populations for PORT Risk Class III/IV subjects, according to the following criteria:

Table 43. Investigator-assigned clinical success/ failure at the TOC and PTE visits

Clinical Success at the EOT assessment was defined as meeting the following: • The subject was alive. • The infection was sufficiently resolved such that further antibacterial therapy was not needed. These subjects may have had some residual changes related to infection (e.g. cough) requiring ancillary (ie, non-antibiotic) treatment, (eg, expectorant). **Clinical Success** at the PTE assessment was defined as meeting the following: • Survival, without receiving any systemic antibacterial other than test article. • Resolution of signs and symptoms of the infection present at Screening with no new symptoms or complications attributable to CABP and no need for further antibacterial therapy. **Clinical Failure** was defined as meeting any of the criteria below: • The subject required alternative antibacterial treatment for CABP prior to EOT related to either (a) progression or development of new symptoms to CABP or (b) development of infectious complications of CABP (eg, empyema, lung abscess) or (c) subject developed an adverse event (AE) that required discontinuation of study therapy prior to the EOT. • The subject received antibacterial therapy that may have been effective for the infection under study for a different infection from the one under study. • The subject died before evaluation. **Indeterminate** was defined as the clinical response to test article could not be adequately inferred because: • The subject was not seen for the assessment because the subject withdrew consent, was lost to follow-up, or other specified reason. • Other specified reason.

Source: applicant's Summary of Clinical Efficacy – CABP.

Secondary efficacy endpoints:

- Microbiological response at EOT and overall microbiological response at PTE (derived from microbiological response at EOT and PTE) per-subject in the micro-mITT and ME-PTE populations.
- Overall microbiological response at PTE (derived from microbiological response at EOT and PTE) according to pathogen in the micro-mITT and ME-PTE populations.

In addition to blood and sputum microscopy and culture, urinary antigen screening (*L. pneumophila*, *P. pneumoniae*) and serology (*L. pneumophila*, *M. pneumoniae*, *C. pneumoniae*) were performed. Blood and sputum isolates always considered a pathogen were: *S. pneumoniae*, *H. influenzae*, *S. aureus*, *M. catarrhalis*, *L. pneumophila*, *M. pneumoniae*, and *C. pneumoniae.* Isolates always considered contaminants were: fungi, *Enterococcus* spp., viridans streptococci, coagulase-negative staphylococci, *Micrococcus* spp., *Neisseria* spp. other than *Neisseria meningitidis*, *Corynebacterium* spp. and other coryneforms, *Lactobacillus* spp., *Vibrio* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Flavobacterium* spp. Other isolates were considered in a blinded case-by-case- manner.

- **Sample size**

For the IACR at PTE endpoint in the ITT population (PORT Risk Class III and IV) assuming an outcome rate of 79% in both treatment groups, non-inferiority margin of 10%, 80% power, and a 1-sided alpha level of 0.0125 (since 1 CABP study was being conducted), using the sample size determination method of Farrington and Manning (1990), a total of 638 subjects (PORT Risk Class III and IV) were required. Assuming an 80% evaluability rate, 510 subjects were available in the CE population. Assuming an 85% response rate in both treatment groups, a 10% non-inferiority margin, 1-sided alpha level of 0.0125, there was 81% power to show non-inferiority for the IACR at PTE in the CE population. If 15% of subjects were in PORT Risk Class II and therefore excluded from the primary efficacy evaluation, a total of 750 subjects were required.

- **Blinding (masking)**

Investigator and sponsor were blinded to treatment allocation. The iv and po phases of the study were double-blind and double-dummy.

- **Statistical methods**

Study populations

- The intent-to-treat (ITT) population consisted of all randomized subjects with PORT Risk Class III/IV, regardless of whether or not the subject received test article. A subject was considered randomized when the IxRS provided the test article assignment (ie, completes a randomization transaction).
- The micro-mITT population consisted of all subjects in the mITT population who had at least 1 causative bacterial pathogen identified at baseline (see above, *Outcomes/endpoints*), according to the more stringent criteria for sputum Gram stain of >25 PMNs/LPF and <10 SECs/LPF.
- The expanded micro-mITT population consisted of all subjects in the mITT population who had at least 1 causative bacterial pathogen identified at baseline (see above, *Outcomes/endpoints*), according to the less stringent criteria for sputum Gram stain of >10 PMNs/LPF and <10 SECs/LPF.
- Two CE analysis sets were defined; the CE-EOT and the CE-PTE comprised mITT patients who received a minimum dose of study drug, completed an outcome assessment, and met all other evaluability criteria detailed in the SAP. By definition, subjects with an indeterminate clinical outcome at the EOT or PTE visits were excluded from the relevant CE population.

Multiplicity

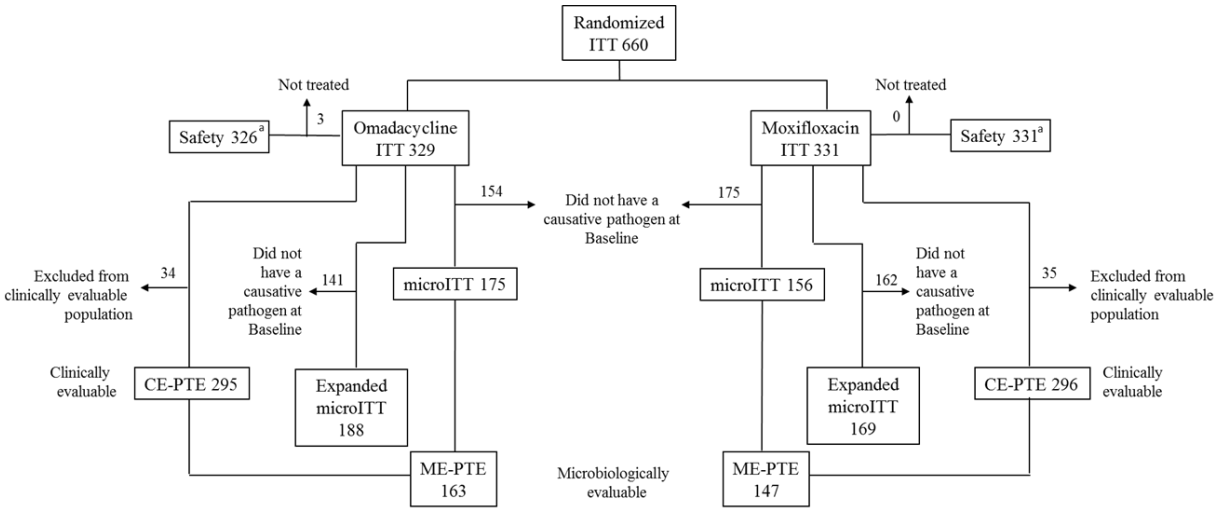
No adjustments were made. Confidence intervals for secondary outcomes were descriptive only.

Missing data

For the IACR at the EOT and PTE visits subjects were defined as an indeterminate if the investigator could not determine whether the subject was a clinical success or failure at the EOT or PTE visits or the subject had a missing response. By definition, subjects with an indeterminate response were included in the denominator for analyses in the ITT and microITT populations, and thus, were considered clinical failures. Subjects with an indeterminate response were excluded from the CE-EOT, CE-PTE, ME-EOT, and ME-PTE populations.

Results (Study PTK0796-CABP-1200)

Figure 6. Participant flow, Study PTK0796-CABP-1200



CE = clinically evaluable, EMA = European Medicines Agency, ITT = intent-to-treat, ME = microbiologically evaluable, microITT = microbiological intent to treat, PORT = Pneumonia Outcomes Research Team, PTE = post therapy evaluation. Source: applicant's Summary of Clinical Efficacy – CABP.

Table 44. Subject disposition, ITT population (Study PTK0796-CABP-1200)

Parameter/ Category	Omadacycline N = 386 n (%)	Moxifloxacin N = 388 n (%)	All Subjects N = 774 n (%)	p-value[a]
Randomized	386 (100.0)	388 (100.0)	774 (100.0)	
Completed study treatment[b]	352 (91.2)	346 (89.2)	698 (90.2)	
Prematurely discontinued from study treatment	34 (8.8)	42 (10.8)	76 (9.8)	0.3981
Reason for premature discontinuation from study treatment				
AE[c]	17 (4.4)	28 (7.2)	45 (5.8)	
Lost to follow-up	0	1 (0.3)	1 (0.1)	
Withdrawal by subject	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[d]	356 (92.2)	362 (93.3)	718 (92.8)	
Prematurely discontinued from study	30 (7.8)	26 (6.7)	56 (7.2)	0.5819
Reason for premature discontinuation from study				
AE[c]	7 (1.8)	9 (2.3)	16 (2.1)	
Lost to follow-up	0	3 (0.8)	3 (0.4)	
Withdrawal by subject	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)	

AE = adverse event; EOT = end of treatment; ITT = intent-to-treat; PTE = post therapy evaluation.

Source: Study PTK0796-CABP-1200 CSR.

- **Conduct of the study**

Database lock: 24 March 2017

Database unblind: 21 March 2017

- **Baseline data, subjects with PORT Risk Class III/IV**

Table 45. Demographics in the Safety population (Study PTK0796-CABP-1200)

Characteristics	Omadacycline N = 386	Moxifloxacin N = 388	All Subjects N = 774	p-value[a]
Gender, n (%)				
n	386	388	774	
Female	178 (46.1)	169 (43.6)	347 (44.8)	
Male	208 (53.9)	219 (56.4)	427 (55.2)	0.5154
Race, n (%)				
n	386	388	774	
White	356 (92.2)	355 (91.5)	711 (91.9)	
Black or African American	11 (2.8)	7 (1.8)	18 (2.3)	
Asian	17 (4.4)	18 (4.6)	35 (4.5)	
American Indian or Alaska Native	0	2 (0.5)	2 (0.3)	
Native Hawaiian or Other Pacific Islander	0	0	0	
Other	2 (0.5)	6 (1.5)	8 (1.0)	0.3319
Ethnicity, n (%)				
n	386	388	774	
Hispanic or Latino	10 (2.6)	14 (3.6)	24 (3.1)	
Not Hispanic or Latino	372 (96.4)	370 (95.4)	742 (95.9)	
Not reported/unknown	4 (1.0)	4 (1.0)	8 (1.0)	0.7282
Age (years)				
n	386	388	774	
Mean (SD)	60.9 (15.24)	62.1 (15.21)	61.5 (15.23)	
Median	61.0	63.0	62.0	
Min, max	19, 97	19, 94	19, 97	0.1491
Categorical age (years), n (%)				
n	386	388	774	
18-45	62 (16.1)	61 (15.7)	123 (15.9)	
> 45-65	172 (44.6)	155 (39.9)	327 (42.2)	
> 65	152 (39.4)	172 (44.3)	324 (41.9)	0.3474
> 75	75 (19.4)	83 (21.4)	158 (20.4)	
Height (cm)				
n	386	388	774	
Mean (SD)	168.6 (9.876)	168.5 (9.844)	168.5 (9.854)	
Median	169.00	168.00	169.00	
Min, max	137.2, 196.0	135.0, 198.0	135.0, 198.0	0.8800
Weight (kg)				
n	386	388	774	
Mean (SD)	77.58 (17.979)	78.00 (17.861)	77.79 (17.910)	
Median	76.00	77.50	77.00	
Min, max	36.0, 147.0	28.0, 145.2	28.0, 147.0	0.9142
BMI (kg/m^2)				
n	386	388	774	
Mean (SD)	27.23 (5.75)	27.42 (5.79)	27.33 (5.77)	
Median	26.3	26.5	26.4	
Min, max	16, 51	13, 55	13, 55	0.5724
CrCL (local lab), n (%)				
n	386	388	774	
Normal renal function (> 80 mL/minute)	187 (48.4)	207 (53.4)	394 (50.9)	
Mild renal impairment (> 50-80 mL/minute)	128 (33.2)	119 (30.7)	247 (31.9)	
Moderate renal impairment (30-50 mL/minute)	70 (18.1)	62 (16.0)	132 (17.1)	
Severe renal impairment (< 30 mL/minute)	1 (0.3)	0	1 (0.1)	0.4020

Source: Study PTK0796-CABP-1200 CSR Table 10.

Table 46. Medical history occurring in >10% of Safety population (Study PTK0796-ABSI-16301)

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

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

Source: Study PTK0796-CABP-1200 CSR Table 11.

Two thirds of subjects were in PORT Risk Class III and the remaining third were in PORT Risk Class IV. The mean PORT score was approximately 87. One third of patients had moderate to severe CABP based on their CURB-65 score or American Thoracic Society (ATS) criteria.

The proportion of subjects receiving iv treatment with a calculated treatment compliance of ≥ 80% for the omadacycline and moxifloxacin groups was 98.5% and 99.4%, respectively in the ITT population and 100% in both groups in the CE-PTE population.

The proportion of subjects receiving po treatment with a calculated treatment compliance of ≥ 80% for the omadacycline and moxifloxacin groups was 76.0% and 73.7%, respectively in the ITT population and 79.0% and 75.3%, respectively in the CE-PTE population. Oral compliance may have been lower due to the administration of study drug in the outpatient setting. It is unlikely that the lower oral compliance had any clinically meaningful impact since the efficacy at PTE was high and a majority of patients (~75%) switched to oral therapy.

- **Causative organisms**

Table 47. CABP Subjects, most prevalent organisms, microITT Population, subjects with PORT Risk Class III/IV (PTK0796-CABP-1200)

Baseline Pathogen	Omadacycline (N=175) n (%)	Moxifloxacin (N=156) n (%)
Gram-Positive Bacteria (aerobes)	55 (31.4)	51 (32.7)
Streptococcus pneumoniae	39 (22.3)	32 (20.5)
PSSP	24 (13.7)	20 (12.8)
Macrolide Resistant	10 (5.7)	5 (3.2)
MDRSP	7 (4.0)	6 (3.8)
Staphylococcus aureus	10 (5.7)	9 (5.8)
MSSA	10 (5.7)	8 (5.1)
Gram-Negative Bacteria (aerobes)	67 (38.3)	60 (38.5)
Haemophilus influenzae	26 (14.9)	14 (9.0)
Haemophilus parainfluenzae	14 (8.0)	13 (8.3)
Klebsiella pneumoniae	13 (7.4)	11 (7.1)
Escherichia coli	4 (2.3)	6 (3.8)
Pseudomonas aeruginosa	3 (1.7)	3(1.9)

Baseline Pathogen	Omadacycline (N=175) n (%)	Moxifloxacin (N=156) n (%)
Atypical Pathogens	104 (59.4)	91 (58.3)
Mycoplasma pneumoniae	63 (36.0)	50 (32.1)
Legionella pneumophila	31 (17.7)	32 (20.5)
Chlamydia pneumoniae	26 (14.9)	24 (15.4)

MDR = multi-drug resistant, MDRSP = multidrug-resistant *S. pneumoniae,* microITT = microbiological intent-to-treat, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S. aureus*, N = Number of subjects in the microITT population, n = Number of subjects within a specific category, PORT = Pneumonia Outcomes Research Team, PSSP = penicillin-susceptible *S. pneumoniae*.
Source: adapted from applicant's Summary of Clinical Pharmacology Studies – Special Studies – Microbiology.

Table 48. Omadacycline and Moxifloxacin MIC Summary Statistics for Baseline Pathogens From Blood and/or Respiratory Cultures, microITT population, subjects with PORT Risk Class III/IV (Study PTK0796-CABP-1200)

	Omadacycline (N=175)			Moxifloxacin (N=156)		
Baseline Pathogen	n	Range (µg/mL)	MIC_{50}/ MIC_{90} (µg/mL)	n	Range (µg/mL)	MIC_{50}/ MIC_{90} (µg/mL)
Gram-positive organisms (aerobes)	42	0.015 - 0.25	0.06/0.12	40	≤ 0.03-4	0.12/0.25
Streptococcus pneumoniae	26	0.015 - 0.12	0.03/0.06	22	≤ 0.03 - 0.25	0.12/0.12
MDRSP	7	0.03 - 0.12	NC	6	≤ 0.03 - 0.25	NC
PSSP	25	0.015 - 0.12	0.03/0.06	20	0.06 - 0.25	0.12/0.12
Macrolide Resistant	10	0.03 - 0.12	0.03/0.06	5	0.06 - 0.25	NC
Staphylococcus aureus	10	0.12 - 0.25	0.12/0.25	9	0.03 – 0.06	NC
MSSA	10	0.12 - 0.25	0.12/0.25	8	0.03 – 0.06	NC
Gram-negative organisms (aerobes)	66	0.12 - > 16	2/8	56	≤ 0.004 - > 4	0.12/1
Haemophilus influenzae	26	1-2	1/2	13	0.008 - 1	0.03/0.06
Haemophilus parainfluenzae	13	1 - 4	2/4	12	≤ 0.004 - 1	0.12/0.25
Klebsiella pneumoniae	12	1 – 16	2/16	11	0.06 - 0.12	0.12/0.12
Escherichia coli	4	0.5 – 4	NC	6	0.03 - > 4	NC
Pseudomonas aeruginosa	3	4 - > 16	NC	3	0.06 - 1	NC

Source: Study PTK0796-CABP-1200 CSR Table 20.

- **Numbers analysed**

Table 49. Analysis populations Overall and by Geographic Region, subjects with PORT Risk Class III/IV (Study PTK0796-CABP-1200)

Region	Population	Omadacycline		Moxifloxacin		All Subjects	
		n	(%)	n	(%)	N	(%)
Overall	**ITT**	**329**		**331**		**660**	
	Safety	326	(99.1)	331	(100)	657	(99.5)
	micro-mITT	175	(53.2)	156	(47.1)	331	(50.2)
	Expanded micro-mITT	188	(57.1)	169	(51.1)	357	(54.1)
	CE-EOT	309	(93.9)	307	(92.7)	616	(93.3)
	CE-PTE	295	(89.7)	296	(89.4)	591	(89.5)
	ME-EOT	167	(50.8)	151	(45.6)	318	(48.2)
	ME-PTE	163	(49.5)	147	(44.4)	310	(47.0)
Western Europe	**ITT**	**77**		**70**		**147**	
	Safety	76	(98.7)	70	(100.0)	146	(99.3)
	micro-mITT	39	(50.6)	28	(40.0)	67	(45.6)
	Expanded micro-mITT	40	(51.9)	29	(41.4)	69	(46.9)

	CE-EOT	72	(93.5)	62	(88.6)	134	(91.2)
	CE-PTE	71	(92.2)	62	(88.6)	133	(90.5)
	ME-EOT	35	(45.5)	26	(37.1)	61	(41.5)
	ME-PTE	34	(44.2)	26	(37.1)	60	(40.8)
Eastern Europe	**ITT**	**209**		**213**		**422**	
	Safety	208	(99.5)	213	(1 000)	421	(99.8)
	micro-mITT	116	(55.5)	111	(52.1)	227	(53.8)
	Expanded micro-mITT	127	(60.8)	122	(57.3)	249	(59.0)
	CE-EOT	196	(93.8)	203	(95.3)	399	(94.5)
	CE-PTE	186	(89.0)	194	(91.1)	380	(90.0)
	ME-EOT	112	(53.6)	108	(50.7)	220	(52.1)
	ME-PTE	109	(52.2)	104	(48.8)	213	(50.5)
North America (USA, Mexico)	**ITT**	**0**		**3**		**3**	
	Safety	0		3	(100.0)	1	(33.3)
	micro-mITT	0		0		0	
	Expanded micro-mITT	0		0		0	
	CE-EOT	0		2	(66.7)	2	(66.7)
	CE-PTE	0		1	(33.3)	1	(33.3)
	ME-EOT	0		0		0	
	ME-PTE	0		0		0	
Rest of World	**ITT**	**43**		**45**		**88**	
	Safety	42	(97.7)	45	(100.0)	87	(98.9)
	micro-mITT	20	(46.5)	17	(37.8)	37	(42.0)
	Expanded micro-mITT	21	(48.8)	18	(40.0)	39	(44.3)
	CE-EOT	41	(95.3)	40	(88.9)	81	(92.0)
	CE-PTE	38	(88.4)	39	(86.7)	77	(87.5)
	ME-EOT	20	(46.5)	17	(37.8)	37	(42.0)
	ME-PTE	20	(46.5)	17	(37.8)	37	(42.0)

Table compiled by assessor. Source data: Study PTK0796-CABP-1200 CSR Table 14.1.1.2E.

- **Outcomes and estimation**

Primary efficacy analysis

Table 50. Overall Clinical Response at the PTE in ITT and CE-PTE populations, subjects with PORT Risk Class III/IV (Study PTK0796-CABP-1200)

Efficacy Outcome	Omadacycline n (%)	Moxifloxacin n (%)	Difference (97.5% CI)
ITT	**N = 329**	**N = 331**	
Clinical success	291 (88.4)	282 (85.2)	3.3 (-2.7, 9.3)
Clinical failure or indeterminate	38 (11.6)	49 (14.8)	
Clinical failure	27 (8.2)	35 (10.6)	
Rescue/ alternative antibacterial required for CABP	6 (1.8)	9 (2.7)	
Infectious complication of CABP	2 (0.6)	2 (0.6)	
Potentially effective antibacterial received for different indication	3 (0.9)	3 (0.9)	
Died before evaluation	3 (0.9)	3 (0.9)	
Clinical failure at EOT	22 (6.7)	30 (9.1)	
Rescue/ alternative antibacterial required for CABP	12 (3.6)	19 (5.7)	
Infectious complication of CABP	2 (0.6)	5 (1.5)	
AE requiring discontinuation of test article	4 (1.2)	8 (2.4)	
Potentially effective antibacterial received for different indication	1 (0.3)	1 (0.3)	
Died before evaluation	3 (0.9)	1 (0.3)	
Indeterminate	11 (3.3)	14 (4.2)	
CE-PTE	**N = 295**	**N = 296**	
Clinical success	273 (92.5)	268 (90.5)	2.0 (-3.2, 7.4)
Clinical failure	22 (7.5)	28 (9.5)	

CE = clinically evaluable, CI = confidence interval, CSR = clinical study report, EMA = European Medicines Agency, EOT = end of treatment, ITT = intent-to-treat, PORT = Pneumonia Outcomes Research Team, PTE = post therapy evaluation.
Source: amalgamated from Study PTK0796-CABP-1200 EMA CSR Tables 14.2.2.1.1E and 14.2.2.2.1E.

Given that the lower limit of the 97.5% CI for the treatment difference between arms in the ITT and CE populations was above the pre-specified margin of -10%, omadacycline was considered non-inferior to moxifloxacin. Sensitivity analysis of the primary outcome conducted by constructing an unstratified 97.5% CI yielded results almost identical to the primary analysis in both the ITT (97.5% CI: -2.7, 9.3) and CE-PTE populations (97.5% CI: -3.2, 7.3).

Of note, the lower limit of a 99% CI was also higher than -10% (-3.6% for ITT population and -4.0% for CE-PTE population).

Secondary efficacy analyses

Microbiological response (per-subject)

Nearly all cases of microbiological eradication were "presumed" (i.e. there were very few post-baseline cultures performed) in the micro-mITT.

Table 51. Microbiological response at EOT and PTE in microITT, ME-EOT and ME-PTE populations, subjects with PORT Risk Class III/IV (Study PTK0796-CABP-1200)

Visit/Outcome	Omadacycline n (%)	Moxifloxacin n (%)	Difference (97.5% CI)
microITT	N = 175	N = 156	
Microbiological response at EOT visit			
Favourable	160 (91.4)	145 (92.9)	-1.5 (-8.5, 5.6)
Eradication	4 (2.3)	8 (5.1)	
Presumed eradication	156 (89.1)	137 (87.8)	
Unfavourable	13 (7.4)	9 (5.8)	
Persistence	1 (0.6)	1 (0.6)	
Presumed persistence	12 (6.9)	8 (5.1)	
Indeterminate	2 (1.1)	2 (1.3)	
Overall microbiological response at PTE visit			
Favourable	158 (90.3)	138 (88.5)	1.8 (-5.9, 9.9)
Eradication	2 (1.1)	3 (1.9)	
Presumed eradication	156 (89.1)	135 (86.5)	
Unfavourable	15 (8.6)	14 (9.0)	
Persistence	1 (0.6)	1 (0.6)	
Presumed persistence	14 (8.0)	13 (8.3)	
Indeterminate	2 (1.1)	4 (2.6)	
ME-EOT	N = 167	N = 151	
Microbiological response at EOT visit			
Favourable	156 (93.4)	144 (95.4)	-2.0 (-8.3, 4.4)
Eradication	4 (2.4)	8 (5.3)	
Presumed eradication	152 (91.0)	136 (90.1)	
Unfavourable	11 (6.6)	7 (4.6)	
Persistence	1 (0.6)	1 (0.7)	
Presumed persistence	10 (6.0)	6 (4.0)	
ME-PTE	N = 163	N = 147	
Overall microbiological response at PTE visit			
Favourable	150 (92.0)	134 (91.2)	0.9 (-6.5, 8.5)
Eradication	1 (0.6)	3 (2.0)	
Presumed eradication	149 (91.4)	131 (89.1)	
Unfavourable	13 (8.0)	13 (8.8)	
Persistence	1 (0.6)	1 (0.7)	
Presumed persistence	12 (7.4)	12 (8.2)	

CABP = community-acquired bacterial pneumonia, CI = confidence interval, CSR = clinical study report, EMA = European Medicines Agency, EOT = end of treatment, ME = microbiologically evaluable, microITT = microbiological intent-to-treat, PTE = post therapy evaluation.
Source: Study PTK0796-CABP-1200 EMA CSR.

Microbiological response (per-pathogen)

There was a numerically lower response rate for omadacycline against *H. influenzae*, when comparing the overall microbiological response according to pathogen. The absolute numbers are small and therefore must be interpreted with caution. Of the 4 omadacycline subjects with *H. influenzae* who had an unfavourable microbiological response, one was indeterminate and one subject died before evaluation.

Table 52. Overall Microbiological Favourable Response at PTE Visit by Baseline Pathogen isolated in ≥ 10 Subjects, microITT Population, subjects with PORT Risk Class III/IV (Study PTK0796-CABP-1200)

	Omadacycline N = 175		Moxifloxacin N = 156	
Baseline Pathogen	**N1**	**Favorable Response n (%)**	**N1**	**Favorable Response n (%)**
Gram-positive bacteria (aerobes)	55	49 (89.1)	51	44 (86.3)
Streptococcus pneumoniae	39	35 (89.7)	32	29 (90.6)
PSSP	24	22 (91.7)	20	19 (95.0)
Macrolide-resistant	10	10 (100.0)	5	5 (100.0)
Staphylococcus aureus	10	8 (80.0)	9	7 (77.8)
MSSA	10	8 (80.0)	8	6 (75.0)
Gram-negative bacteria (aerobes)	67	57 (85.1)	60	51 (85.0)
Haemophilus influenzae	26	22 (84.6)	14	14 (100.0)
Haemophilus parainfluenzae	14	11 (78.6)	13	11 (84.6)
Klebsiella pneumoniae	13	10 (76.9)	11	9 (81.8)
Atypical pathogens	104	97 (93.3)	91	84 (92.3)
Mycoplasma pneumoniae	63	60 (95.2)	50	45 (90.0)
Legionella pneumophila	31	30 (96.8)	32	31 (96.9)
Chlamydophila pneumoniae	26	23 (88.5)	24	22 (91.7)

N1 = number of subjects in the microITT population with the baseline pathogen.
n = number of subjects in the microITT population with a favorable microbiological response at the EOT visit.
Percentages were based on the number of subjects in N1.
A favorable microbiological response was a response of eradication or presumed eradication at the EOT visit.
Subjects with a baseline pathogen from UAT or serology could only have a presumed response.
Includes pathogens identified in ≥ 10 subjects in either treatment group.
EOT = end of treatment, microITT = microbiological intent-to-treat, MSSA = methicillin-susceptible *Staphylococcus aureus*, PORT = Pneumonia Outcomes Research Team, PSSP = penicillin-susceptible *Streptococcus pneumoniae*, PTE = post therapy evaluation, UAT = urinary antigen test.

Source: Study PTK0796-CABP-1200 EMA CSR Table 21.

Additional efficacy analyses

Mono- and poly-microbial infections

Table 53. Overall Microbiological Response at PTE Visit by Mono-microbial and Poly-microbial Infection, microITT Population (Study PTK0796-CABP-1200)

Mono- and Poly-microbial Pathogens Overall Microbiological Response	Omadacycline (N=204) n (%)	Moxifloxacin (N=182) n (%)
Mono-microbial Gram-positive Pathogen, N1	30	23
Favorable	27 (90.0)	21 (91.3)
Unfavorable	2 (6.7)	1 (4.3)
Indeterminate	1 (3.3)	1 (4.3)
Mono-microbial Gram-Negative Pathogen, N1	37	34
Favorable	34 (91.9)	25 (73.5)
Unfavorable	3 (8.1)	7 (20.6)
Indeterminate	0	2 (5.9)
Poly-microbial Gram-positive Pathogens, N1	1	2
Favorable	1 (100.0)	0
Unfavorable	0	1 (50.0)
Indeterminate	0	1 (50.0)
Poly-microbial Gram-Negative Pathogens, N1	5	7
Favorable	3 (60.0)	6 (85.7)
Unfavorable	2 (40.0)	1 (14.3)
Only Atypical Pathogens, N1	80	68
Favorable	75 (93.8)	65 (95.6)
Unfavorable	5 (6.3)	3 (4.4)
Mixed Gram-positive and Gram-negative Pathogens, N1	13	10
Favorable	10 (76.9)	9 (90.0)
Unfavorable	2 (15.4)	0
Indeterminate	1 (7.7)	1 (10.0)
Mixed Gram-positive and Atypical Pathogens, N1	14	18
Favorable	13 (92.9)	16 (88.9)
Unfavorable	1 (7.1)	2 (11.1)
Mixed Gram-negative and Atypical Pathogens, N1	21	17
Favorable	19 (90.5)	13 (76.5)
Unfavorable	2 (9.5)	4 (23.5)
Mixed Gram-positive, Gram-negative and Atypical Pathogens, N1	3	3
Favorable	2 (66.7)	3 (100.0)
Unfavorable	1 (33.3)	0

Source: Study PTK0796-CABP-1200 EMA CSR Table 14.2.11.1.

Clinical outcome according to baseline pathogen and/or MIC

Generally, clinical success rates in CABP were high across *S. pneumoniae*, *Enterobacteriacae* and atypical infections, regardless of resistance to other antibiotic classes. Slightly lower success rates were seen with *S. aureus* and *Haemophilus* spp. infections. Clinical success rates were not demonstrably correlated to omadacycline MIC, indeed clinical success was reported in omadacycline subjects with baseline pathogens with MIC up to 16 µg/mL. Susceptibility data were not obtained for atypical pathogens.

Table 54. Clinical Success at PTE by Pathogen and Study Drug Received MIC (µg/mL) in CABP, microITT population, subjects with PORT Risk Class III/IV (Study PTK0796-CABP-1200)

	Omadacycline (N=175)		Moxifloxacin (N=156)	
Baseline Pathogen	**Baseline MIC (µg/mL)**	**Clinical Success n/total (%)**	**Baseline MIC (µg/mL)**	**Clinical Success n/total (%)**
Gram-positive organisms (aerobes)				
Streptococcus pneumoniae		26		22
	0.015	2/2 (100.0)	≤0.03	1/1 (100.0)
	0.03	12/14 (85.7)	0.06	5/5 (100.0)
	0.06	9/9 (100.0)	0.12	14/15 (93.3)
	0.12	1/1 (100.0)	0.25	1/1 (100.0)
Penicillin-susceptible *S. pneumoniae*		25		20
	0.015	2/2 (100.0)	0.06	5/5 (100.0)
	0.03	12/14 (85.7)	0.12	13/14 (92.9)
	0.06	8/8 (100.0)	0.25	1/1 (100.0)
	0.12	1/1 (100.0)	0.5	0
Macrolide Resistant		10		5
	0.03	6/6 (100.0)	0.06	2/2 (100.0)
	0.06	3/3 (100.0)	0.12	2/2 (100.0)
	0.12	1/1 (100.0)	0.25	1/1 (100.0)
Staphylococcus aureus		10		9
	0.12	5/8 (62.5)	0.03	6/7 (85.7)
	0.25	2/2 (100.0)	0.06	1/2 (50.0)
MSSA		10		8
	0.12	5/8 (62.5)	0.03	5/6 (83.3)
	0.25	2/2 (100.0)	0.06	1/2 (50.0)
Gram-negative organisms (aerobes)				
Haemophilus influenzae		26		13
	0.5	0	0.008	1/1 (100.0)
	1	13/15 (86.7)	0.015	5/5 (100.0)
	2	8/11 (72.7)	0.03	4/4 (100.0)
	4	0	0.06	2/2 (100.0)
	>4	0	1	1/1 (100.0)
Haemophilus parainfluenzae		13		12
	≤0.008	0	≤0.004	1/1 (100.0)
	0.25	0	0.03	1/1 (100.0)
	0.5	0	0.06	1/1 (100.0)
	1	2/3 (66.7)	0.12	5/5 (100.0)
	2	5/7 (71.4)	0.25	2/3 (66.7)
	4	3/3 (100.0)	1	0/1 (0.0)
Klebsiella pneumoniae		12		11
	1	2/2 (100.0)	0.06	4/4 (100.0)
	2	5/7 (71.4)	0.12	5/7 (71.4)
	4	0	0.25	0
	8	1/1 (100.0)	0.5	0
	16	2/2 (100.0)	1	0
Escherichia coli		4		6
	0.5	1/1 (100.0)	0.03	1/1 (100.0)
	1	1/2 (50.0)	0.06	2/3 (66.7)
	2	0	0.12	0/1 (0.0)
	4	0/1 (0.0)	0.5	0
	>4	0	>4	1/1 (100.0)
Atypical Pathogens[a]	NA		NA	
Mycoplasma pneumoniae		60/63 (95.2)		45/50 (90.0)
Legionella pneumophila		30/31 (96.8)		31/32 (96.9)
Serology		28/29 (96.6)		29/30 (96.7)

	Omadacycline (N=175)		Moxifloxacin (N=156)	
Baseline Pathogen	Baseline MIC (µg/mL)	Clinical Success n/total (%)	Baseline MIC (µg/mL)	Clinical Success n/total (%)
Urinary Antigen		5/5 (100.0)		7/7 (100.0)
Chlamydia pneumoniae		23/26 (88.5)		22/24 (91.7)

MIC = minimum inhibitory concentration, microITT = microbiological intent-to-treat,
MSSA = methicillin-susceptible *S. aureus*, NA=not available.
Source: adapted from applicant's Summary of Clinical Pharmacology Studies – Special Studies – Microbiology.

New and super-infections

Table 55. New and super-infections (Study PTK0796-CABP-1200)

Subject	Treatment	New or super-infection
411-5003 74F	4d iv omadacycline	*K. pneumoniae* (Day 3), super-infection *P. mirabilis* (Days, 4, 5 6), super-infection and then new infection. Note: subject died (Day 25) due to acute respiratory and multi-organ failure.
311-5012 64F	5d iv omadacycline	*E. cloacae* and *K. oxytoca* (Day 6), new infections
343-5029 69F	10d iv 3d po moxifloxacin	*A. baumannii* (Day 28), new infection
405-4020 73M	6d iv 4d po moxifloxacin	MRSA (Day 10), new infection
551-5009 66F	5d iv moxifloxacin	*M. catarrhalis* (Day 5), new infection

Table compiled by assessor. Source data: Study PTK0796-CABP-1200 EMA CSR 11.5.1.5.8.

Concordance of clinical outcome across visits

The omadacycline arm demonstrated numerically better continuity of cure than moxifloxacin, with 8/270 ECR successes deemed overall failures at PTE in the omadacycline, vs 15/279 ECR successes deemed overall failures PTE in the moxifloxacin arm. The number of ECR successes later deemed indeterminate (including subjects not clinically evaluable) was also lower in the omadacycline arm.

Sub-group analysis (PORT Risk Class)

Sub-group analysis revealed, perhaps unsurprisingly, slightly higher rates of clinical success amongst subjects with PORT Risk Class IV vs III, but the lower limit of the two-sided 97.5% confidence interval was higher than -10% both in ITT population and CE-PTE populations, for both Class III and IV:

Table 56. Overall Clinical Response at the PTE by PORT Risk Class, ITT and CE-PTE Populations, subjects with PORT Risk Class III (Study PTK0796-CABP-1200)

Population	Efficacy Outcome	Omadacycline n (%)	Moxifloxacin n (%)	Difference (97.5% CI)[a]
ITT		(N=227)	(N=216)	
	Clinical Success	206 (90.7)	190 (88.0)	2.8 (-3.9, 9.7)
	Clinical Failure or Indeterminate	21 (9.3)	26 (12.0)	
	Clinical Failure	16 (7.0)	18 (8.3)	
	Indeterminate	5 (2.2)	8 (3.7)	
CE-PTE		(N=204)	(N=202)	
	Clinical Success	191 (93.6)	186 (92.1)	1.5 (-4.4, 7.7)
	Clinical Failure	13 (6.4)	16 (7.9)	

Source: Applicant's responses to D120 LoQ Q210.

Table 57. Overall Clinical Response at the PTE by PORT Risk Class, ITT and CE-PTE Populations, subjects with PORT Risk Class IV (Study PTK0796-CABP-1200)

Population	Efficacy Outcome	Omadacycline n (%)	Moxifloxacin n (%)	Difference (97.5% CI)[a]
ITT		(N=102)	(N=115)	
	Clinical Success	85 (83.3)	92 (80.0)	3.3 (-8.8, 15.2)
	Clinical Failure or Indeterminate	17 (16.7)	23 (20.0)	
	Clinical Failure	11 (10.8)	17 (14.8)	
	Indeterminate	6 (5.9)	6 (5.2)	
CE-PTE		(N=91)	(N=94)	
	Clinical Success	82 (90.1)	82 (87.2)	2.9 (-8.2, 14.0)
	Clinical Failure	9 (9.9)	12 (12.8)	

Source: Applicant's responses to D120 LoQ Q210.

Sub-group analysis (prior antibiotic use)

Sub-group analysis revealed slightly lower rates of clinical success amongst subjects who had not received a single dose of short-acting antibiotic prior to study randomisation, as might be expected, however the difference was less dramatic in the omadacycline arm than the moxifloxacin arm:

Table 58. Overall Clinical Response at the PTE by PORT Risk Class, ITT Population, subjects with PORT Risk Class III/IV (Study PTK0796-CABP-1200)

Efficacy Outcome/Prior Antibiotic Use	Omadacycline N = 329 n (%)	Moxifloxacin N = 331 n (%)	Difference (97.5% CI)[a]
Yes – received prior antibiotics	72	72	-
Clinical success	65 (90.3)	65 (90.3)	0.0 (-12.1, 12.1)
No – did not receive prior antibiotics	257	259	-
Clinical success	226 (87.9)	217 (83.8)	4.2 (-2.8, 11.2)

Source: Study PTK0796-CABP-1200 EMA CSR Table 25.

Sub-group analysis (other)

Sub-group analyses revealed no obvious differences between treatment arms according to geographic region, baseline bacteraemia, baseline CURB-65 score and for subjects who switched to PO treatment vs subjects who did not switch. Some numerical differences are noted, but small absolute numbers in some of these groups precludes any robust conclusions.

3.3.5.2.4. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 59. Summary of efficacy for pivotal studies

Title: A Phase 3 Randomised, Double-Blind, Multi-Centre Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Linezolid (Zyvox®) IV/PO for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

Study identifier	PTK0796-ABSI-1108	
Design	1:1 randomised, active-controlled, double-blinded Phase 3 non-inferiority study of omadacycline administered iv and po against comparator Linezolid administered iv and po in treatment of ABSSSI known or suspected to be caused by Gram positive pathogens.	
Hypothesis	Non-inferiority (-10%)	
Treatments groups	Omadacycline (n=329)	100 mg iv q12h for 2 doses, then 100 mg iv q24h. Option to switch to 300 mg po q24h after a minimum of 3 days. Total duration 7-14 days.
	Linezolid (n=326)	600 mg iv q12h. Option to switch to 600 mg po q12h after a minimum of 3 days. Total duration 7-14 days.
Endpoints	Co-Primary endpoint	Overall clinical response at PTE (derived from IACR at EOT and PTE) in the mITT and CE-PTE populations
Database lock	09 June 2016	

Results and Analysis

Analysis	**Primary Analysis**		
Co-primary endpoint	**Treatment group**	**Omadacycline**	**Linezolid**
	Number of subjects (mITT)	316	311
	Overall clinical success at PTE in mITT population	86.1%	83.6%
	2.5 (95% CI -3.2, 8.1)		
	Number of subjects (CE-PTE)	269	260
	Overall clinical success at PTE in CE-PTE population	96.3%	93.5%
	2.8 (95% CI -0.9, 7.1)		

Title: A Phase 3 Randomised, Double-Blind, Multi-Centre Study to Compare the Safety and Efficacy of Oral Omadacycline to Oral Linezolid (Zyvox®) for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)	
Study identifier	PTK0796-ABSI-16301

Design	1:1 randomised, active-controlled, double-blinded Phase 3 non-inferiority study of omadacycline administered po against comparator Linezolid administered po in treatment of ABSSSI known or suspected to be caused by Gram positive pathogens.	
Hypothesis	Non-inferiority (-10%)	
Treatments groups	Omadacycline (n=368)	450 mg po q24h for 2 doses, followed by 300 mg po q24h. Total duration 7-14 days.
	Linezolid (n=367)	600 mg po q12h. Total duration 7-14 days.
Endpoints	Co-Primary endpoint	Overall clinical response at PTE (derived from IACR at EOT and PTE) in the mITT and CE-PTE populations
Database lock	30 June 2017	

Results and Analysis

Analysis	**Primary Analysis**		
Co-primary endpoint	**Treatment group**	**Omadacycline**	**Linezolid**
	Number of subjects (mITT)	360	360
	Overall clinical success at PTE in mITT population	84.2%	80.8%
	3.3 (95% CI -2.2, 9.0)		
	Number of subjects (CE-PTE)	284	292
	Overall clinical success at PTE in CE-PTE population	97.9%	95.5%
	2.3 (95% CI -0.5, 5.8)		

Title: A Phase 3 Randomised, Double-Blind, Multi-Centre, Non-inferiority Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Moxifloxacin IV/PO for Treating Adult Subjects with Community-Acquired Bacterial Pneumonia (CABP)	
Study identifier	PTK0796-CABP-1200
Design	1:1 randomised, double-blind, active-comparator-controlled, multi-centre Phase 3 non-inferiority study comparing omadacycline administered iv and po against moxifloxacin administered iv and po for the treatment of adults with CABP.

Hypothesis	Non-inferiority (-10%)	
Treatments groups	Omadacycline (n=329)	100 mg iv q12h for 2 doses, then 100 mg iv q24h. Option to switch to 300 mg po q24h after a minimum of 3 days. Total duration 7-14 days.
	Moxifloxacin (n=331)	400 mg iv q24h . Option to switch to 400 mg po q24h after a minimum of 3 days. Total duration 7-14 days.
Endpoints	Co-Primary endpoint	Overall clinical response at PTE (derived from IACR at EOT and PTE) in the ITT and CE-PTE populations
Database lock	24 March 2017	

Results and Analysis

Analysis	**Primary Analysis**		
Co-primary endpoint	**Treatment group**	**Omadacycline**	**Moxifloxacin**
	Number of subjects (ITT)	329	331
	Overall clinical success at PTE in ITT population	88.4%	85.2%
	3.3 (97.5% CI -2.7, 9.3)		
	Number of subjects (CE-PTE)	295	296
	Overall clinical success at PTE in CE-PTE population	92.5%	90.5%
	2.0 (97.5% CI -3.2, 7.4)		

3.3.6. **Analysis performed across trials (pooled analyses)**

Causative organisms – pooled Phase 3 ABSSSI studies (PTK0796-ABSI-1108 and PTK0796-ABSI-16301)

Table 60. ABSSSI Subjects With Pathogens Identified at Baseline, most prevalent organisms (microITT Population) (Pooled PTK0796-ABSI-1108 and PTK0796-ABSI-16301)

Baseline Pathogen	Omadacycline (N=228) n (%)	Linezolid (N=227) n (%)
Gram-positive organisms (aerobes)	220 (96.5)	219 (96.5)
Staphylococcus aureus	156 (68.4)	151 (66.5)
MRSA	69 (30.3)	50 (22.0)

Baseline Pathogen	Omadacycline (N=228) n (%)	Linezolid (N=227) n (%)
MSSA	88 (38.6)	102 (44.9)
Streptococcus anginosus group	47 (20.6)	37 (16.3)
Gram-negative organisms (aerobes)	28 (12.3)	23 (10.1)
Other	20 (8.8)[a]	21 (9.3)[b]
Klebsiella pneumoniae	6 (2.6)	5 (2.2)
Enterobacter cloacae complex	6 (2.6)	4 (1.8)
Haemophilus parainfluenzae	5 (2.2)	5 (2.2)
Gram-positive organisms (anaerobes)	16 (7.0)	15 (6.6)
Gram-negative organisms (anaerobes)	17 (7.5)	13 (5.7)

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

[a] *Acinetobacter baumannii* (1), *A. baumannii* complex (1), *Eikenella corrodens* (2), *Enterobacter aerogenes* (1), *E. cloacae* (3), *Escherichia coli* (2), *Klebsiella oxytoca* (2), *Morganella morganii* (1), *Proteus mirabilis* (2), *Providencia stuartii* (1), *Pseudomonas aeruginosa* (3), *Serratia liquefaciens* (1).

[b] *E. corrodens* (2), *E. aerogenes* (3), *E. cloacae* (1), *E. coli* (3), *Escherichia hermannii* (1), *K. oxytoca* (1), *M. morganii* (3), *P. mirabilis* (1), *P. stuartii* (2), *P. aeruginosa* (2), *Stenotrophomonas maltophilia* (2).

Source: adapted from applicant's Summary of Clinical Pharmacology Studies – Special Studies – Microbiology.

Clinical outcome by baseline pathogen– pooled Phase 3 ABSSSI studies (PTK0796-ABSI-1108 and PTK0796-ABSI-16301)

Generally, clinical success rates in ABSSSI were high regardless of baseline isolate species or resistance to other antibiotic classes. Notably, clinical success rates with omadacycline were good even for Gram negative species, although absolute numbers of such isolates are small and adjunctive Gram-negative therapy, which may have impacted clinical efficacy, was permitted at the discretion of the investigator in any subject diagnosed with a Gram negative or anaerobic organism (in practice this was only applied to 9 subjects in study 1108, of which 5 were in the omadacycline group, and no subject in 16301.

Clinical outcome by baseline MIC– pooled Phase 3 ABSSSI studies (PTK0796-ABSI-1108 and PTK0796-ABSI-16301)

Clinical success rates were not demonstrably correlated to omadacycline MIC, although this apparent lack of relationship may depend on a high overall clinical success rate and very few isolates identified with extremely high MIC values. Notably, clinical success rates with omadacycline were good (>80%) even for species with MIC up to 4 µg/mL (although absolute numbers of isolates are small).

Increased MIC values and emergent resistance in Phase 3 studies

Emergence of resistance, defined as a 4-fold increase in MIC to test article in any post-baseline isolate, was not observed in any of the three Phase 3 studies (TK0796-PTK0796-CABP-1200, PTK0796-ABSI-1108 and PTK0796-ABSI-16301), although it should be noted that post-baseline cultures were not commonly performed in any of the studies, therefore the value of this analysis is very limited.

3.3.7. **Clinical studies in special populations**

No dedicated clinical studies have been performed in special populations, however older subjects were included in the main clinical efficacy studies.

Table 61. Age Groups (Safety Population, SC23 Pooling Group [ABSSSI+cSSI+CABP Phase 2 and 3 Studies])

[a] Characteristics	[b] Omadacycline (N=1252)	[c] Linezolid (N=869)	[d] Moxifloxacin (N=388)	[e] All Subjects (N=2509)
Age Group (years), n (%)				
n	1252	869	388	2509
18-64	1021 (81.5)	803 (92.4)	205 (52.8)	2029 (80.9)
65-74	120 (9.6)	36 (4.1)	95 (24.5)	251 (10.0)
75-84	83 (6.6)	28 (3.2)	70 (18.0)	181 (7.2)
≥85	28 (2.2)	2 (0.2)	18 (4.6)	48 (1.9)

Pooling group SC23 includes: ABSI-1108, ABSI-16301, cSSI-0702, cSSI-0804, CABP-1200.
The denominator for the percentage is the number of subjects who had that parameter assessed.
Source: Table 222.1

The Applicant has provided the requested data. The vast majority of subjects exposed to omadacycline across the clinical programme were <64 years of age. CABP is a significant problem in elderly patients, and the study population enrolled in study 1200 was reflective of this, comprising 41.9% >65 years of age (20.4% >75 years of age). Meanwhile, ABSSSI is a condition predominantly affecting younger patients, as reflected in the study populations enrolled in studies 1108 and 16301, which make up the larger part of subject exposure in the Phase 3 programme, and which comprised just 10.5% and 4.6%, respectively, >65 years of age. Thus, most of the older subjects exposed to omadacycline in the clinical programme were CABP subjects, which is expected given the epidemiology of the different conditions. Due to the overall size of the clinical programme, the absolute number of older subjects exposed to omadacycline is reasonable (231 subjects >65 years old) and, due to the similarity in study design, these subjects would all have received 7-14 days' treatment according to protocol.

3.3.8. **Supportive studies**

Study PTK0796-CSSI-0702 was a 1:1 randomised, active-controlled, single (evaluator)-blinded, multi-centre US Phase 2 safety and tolerability study of 7-14 days' omadacycline iv and po against comparator linezolid iv and po in treatment of adults with cSSSI. Efficacy assessments were a secondary endpoint. The omadacycline dosing regimen was lower than that tested in the pivotal Phase 3 studies in ABSSSI and was not one of those testing in Monte Carlo simulation. Two thirds of randomised subjects had a diagnosis of major abscess, but other subjects were enrolled with a different spectrum of infections to those included in the pivotal Phase 3 studies in ABSSSI, including infections associated with animal or human bites, second degree burns, removable foreign bodies and acute lower-extremity ulcers, as well as cellulitis associated with comorbidity (diabetes mellitus, arterial or venous insufficiency, immunosuppression). The rates of success according to IACR at TOC were numerically higher for omadacycline both the mITT (98.3% vs 75.6%, difference 13.6 (95% CI 1.3, 26.0)) and CE (98% vs 93.2%, difference 4.8 (95% CI -1.7, 11.4)) populations. However, as this study was not powered for statistical inference, no formal conclusion of non-inferiority can be made. Furthermore, the CE and ME populations were smaller for linezolid, on account of a high number of linezolid subjects who were not clinically evaluable at TOC, which may have driven the difference seen between treatment arms.

Study PTK0796-CSSI-0804 was a 1:1 randomised, active-controlled, double-blinded, multi-centre US Phase 3 study of 7-14 days' omadacycline iv and po against comparator linezolid iv and po in treatment of adults with cSSSI and evidence of a systemic inflammatory response, or a known, specified reason for pre-existing immunosuppression. The dosing regimen was one of those tested in

Monte Carlo simulation, but not the regimen used in the pivotal Phase 3 studies in ABSSSI. Two thirds of randomised subjects had a diagnosis of cellulitis, while other major infection types were wound infection and major abscess (capped at 20%), however, inclusion criteria allowed for infections associated with animal or human bites, second degree burns and removable foreign bodies. Enrolment was terminated prematurely by the sponsor following significant changes to the FDA guidance for cSSSI. Furthermore, several *post hoc* changes were made to the analyses, including a change in primary efficacy endpoint from evaluator-defined to Sponsor-defined clinical response. The rates of Sponsor-defined success at TOC in the ITT and CE populations were high across all analysis populations (>85%). However, as the study was terminated prematurely, is not powered for its pre-defined efficacy endpoint.

As these studies applied different inclusion criteria, dose and efficacy endpoints vs the pivotal studies, they offer very limited support for the overall efficacy of omadacycline in skin infections.

3.3.9. **Discussion on clinical efficacy**

ABSSSI

Design and conduct of main clinical studies

The pivotal Phase 3 trials for ABSSSI were generally appropriately designed to fulfil the requirements for a new antibacterial substance according to current EMA guidance. The two dosing regimens used are not fully supported by the currently presented PTA data , however this is considered mitigated by the sufficient quantity of clinical data demonstrating good outcomes at the required MIC values.

The choice of linezolid as comparator was appropriate, as this is an antibiotic authorised across the EU for ABSSSI caused by Gram positive organisms and available in iv and po formulations. The inclusion criteria were appropriate and major abscess was capped at 30% of subjects, given the significant therapeutic role of surgical drainage in major abscess. There was good representation of all three major infection types (wound infection, cellulitis/erysipelas, major abscess). Other infection types, such as infected leg ulcers, were excluded by the protocol. Only subjects with at least one Gram positive causative pathogen at baseline were included in the efficacy analysis populations. Subjects with pre-existing hepatic, renal, immunological and cardiac disease were excluded by the protocol.Subjects were generally young (<65 years) and the majority of subjects were outpatients who did not have bacteraemia or SIRS.

The primary objective (non-inferiority) and statistical approach (including NI margin of -10% and alpha value of 0.05) were appropriate. A total treatment duration of 7-14 days was permitted (despite a maximum of 10 days' recommended in CHMP Scientific Advice), to match the authorised posology of the chosen comparator, and allow flexibility for longer treatment of difficult infections. However, in practice the majority of patients received 10 days' or fewer treatment.

Although microbiological analyses were included as secondary efficacy analyses, as requested by CHMP, the almost negligible proportion of subjects for whom post-baseline cultures were performed (which is not unusual given that there is little left to sample when ABSSSI is successfully treated) resulted in the vast majority of microbiological outcomes being "presumed" (i.e. linked to clinical response) rather than "documented", limiting the value of these secondary analyses.

Only a minor proportion of subjects in Study PTK0796-ABSI-1108 were enrolled in Europe and PTK0796-ABSI-16301 was entirely US-based. Sub-group analyses revealed no obvious difference in infection type or pathogen organism, or the efficacy of omadacycline, by geographic region. Clinical success with omadacycline was high and comparable to linezolid in both EU and non-EU subjects,

although only an approximate numerical comparison is possible. Overall, the results are considered generalisable to the EU population.

Pregnant women and children <18 years old were also excluded from clinical studies in ABSSSI (a PIP has previously been agreed) were excluded from the clinical studies in ABSSSI. This is reflected in the proposed Product Information.

Efficacy data and additional analyses

In studies PTK0796-ABSI-1108 and PTK0796-ABSI-16301, clinical response rates were high across both treatment arms regardless of baseline pathogen or omadacycline MIC, >80% in the mITT population and >90% in the CE-PTE population. Both studies demonstrated non-inferiority of omadacycline compared to linezolid against a pre-defined margin of -10% for the EMA co-primary efficacy endpoints of overall clinical response at PTE (derived from IACR at EOT and PTE) in the mITT and CE-PTE populations. The results of all sensitivity analyses, including analysis of the co-primary endpoint in the all-treated population (as recommended by CHMP Scientific Advice) and analysis treating indeterminate clinical response as clinical success (to assess the impact of missing data) were supportive of the primary analysis. Most patients also underwent a protocol-allowed surgical procedure (which is standard practice in the treatment of ABSSSI). There are no obvious differences in efficacy trends between subjects who did and did not receive surgical intervention.

CABP

Design and conduct of main clinical studies

Study PTK0796-CABP-1200 was designed as a single pivotal study in CABP. The dosing regimen used is not supported by the currently presented PTA data.

The study population (ITT=660) comprised moderate two thirds PORT Risk Class III and one third PORT Risk Class IV in inpatients (mean age >60 years) with moderate to severe CABP and clinically significant medical comorbidities. The dominant pathogens were *M. pneumoniae* (one third of subjects)*, S. pneumoniae* (around 20%), and *H. influenzae* (around 12%), with over half of subjects having an atypical causative organism. The majority (>85%) of subjects were recruited in Europe, making this generally a good representation of EU patients with CABP.

EMA guidance recommends that for studies of IV administration, a minimum of 25% (and ideally 50%) of patients are in class IV-V, accepting that PORT Risk Class V patients requiring ICU admission may be excluded. Subjects with PORT Risk Class V were excluded from the single pivotal trial in CABP on the basis of significant differences in clinical condition and management vs lower PORT Risk Classes, according to the Applicant.

The choice of moxifloxacin as comparator was appropriate, as this is an antibiotic authorised across the EU for CABP and available in iv and po formulations. The inclusion criteria were appropriate, requiring 3 symptoms, 2 vital signs, 1 clinical or laboratory sign, and radiographic confirmation of CABP. Subjects with CABP known to be caused by a pathogen resistant to either test article (including *K. pneumoniae*) were excluded by the protocol. Subjects with pre-existing hepatic, renal, immunological and cardiac disease, and; subjects with pre-existing (and possible pre-disposing) respiratory conditions (including lung neoplasm, aspiration, CF, active TB, bronchiectasis, COPD) or chronic neurological disorders affecting airway clearance, were excluded by the protocol. The majority of subjects did not have bacteraemia (<5%).

The primary objective (non-inferiority) and statistical approach (including NI margin of -10% and alpha value of 0.025) were appropriate. A total treatment duration of 7-14 days was permitted (despite a

maximum of 10 days' recommended in CHMP Scientific Advice), to match the authorised posology of the chosen comparator, and allow flexibility for longer treatment of difficult infections. However, in practice the majority of patients received 10 days' or fewer treatment.

The vast majority of microbiological outcomes were "presumed" (i.e. linked to clinical response) rather than "documented", limiting the value of the microbiological analyses as secondary analyses.

Pregnant women and children <18 years old were also excluded from clinical studies in ABSSSI (a PIP has previously been agreed) were excluded from the clinical studies in ABSSSI. This is reflected in the proposed Product Information.

Efficacy data and additional analyses

Clinical response rates were high, >85% in the ITT population and >90% in the CE-PTE population. The study demonstrated non-inferiority of omadacycline against a pre-defined margin of -10% for the EMA co-primary efficacy endpoints of overall clinical response at PTE in the ITT and CE-PTE populations. The results of sensitivity analysis were supportive of the primary analysis.

Sub-group analysis revealed a numerically higher rate of clinical success in subjects with PORT Risk Class III vs IV, and better rates of clinical success amongst subjects who had not received a single dose of short-acting antibiotic prior to study randomisation in the omadacycline arm.

Clinical success rates in CABP were high regardless of baseline isolate species or resistance to other antibiotic classes. Clinical success rates were not demonstrably correlated to omadacycline MIC. Susceptibility data were not obtained for atypical pathogens.

Conclusions on clinical efficacy

The applicant has presented the results of two pivotal studies in ABSSI in adults and one pivotal study in CABP in adults, all three of which met their primary objective of demonstrating non-inferiority against an authorised comparator according to pre-specific primary analysis agreed with CHMP. A Phase 2 study and a sponsor-terminated Phase 3 study, both in cSSSI, offer only very limited support.

Overall, there is sufficient evidence from two adequately-sized clinical studies for good clinical outcomes in ABSSSI at suitable MIC values, despite lack of comprehensive PK-PD support for efficacy of the proposed dose.

However, the evidence for the CAP indication comes solely from a single pivotal study. These deficiencies mean that Study PTK0796-CABP-1200 has not fulfilled the requirements of a single pivotal study, the objective of which is to confirm an established hypothesis (**MO**).

3.3.10. **Clinical safety**

Safety data were derived from 27 studies in the frame of the phase 1 to 3 programme. The evaluation of omadacycline safety is specifically based on the safety data available from 5 studies, i.e. 1 phase 2 study (CSSI-0702) and 4 phase 3 studies (CSSI-0804, ABSI-1108, ABSI-16301 and CABP-1200), including 1252 subjects who received omadacycline. These studies included a total of 705 subjects who received the intravenous (iv) to oral (po) regimen in each targeted indication, as well as 368 subjects who received the oral-only regimen for the treatment of ABSSSI.

Pooling strategy

The integrated analysis of omadacycline safety data is based on 5 pooled populations:

1) 2 pivotal Phase 3 studies performed in ABSSSI patients **(A3 Pool)**
2) Pivotal Phase 3 studies in ABSSSI combined with 2 supportive studies in cSSSI **(S23 Pool)**

3) the pivotal Phase 3 study investigating CABP **(C3 Pool)**

4) the 3 pivotal Phase 3 studying ABSSSI and CABP **(AC3 Pool)**

5) all studies pool **(SC23 Pool)** comprising the 2 supportive studies in cSSSI and the 3 pivotal Phase 3 studies in ABSSSI and CABP

Table S1 Studies incorporated in the 5 study pools used for the integrated safety analysis

Analysis Pool	Omadacycline All Doses (iv + po)	Linezolid 600 mg (iv + po)	Moxifloxacin 400 mg (iv + po)	Total
Phase 3 ABSSSI studies (A3)	**691**	**689**	-	**1380**
ABSI-1108	323	322	-	645
ABSI-16301	368	367	-	735
Phase 2/3 ABSSSI and cSSSI studies (S23)	**870**	**869**	-	**1739**
ABSI-1108	323	322	-	645
ABSI-16301	368	367	-	735
CSSI-0702	111	108	-	219
CSSI-0804	68	72	-	140
Phase 3 CABP study (C3)	**382**	-	**388**	**770**
CABP-1200	382	-	388	770
Phase 3 ABSSSI and CABP studies (AC3)	**1073**	**689**	**388**	**2150**
ABSI-1108	323	322	-	645
ABSI-16301	368	367	-	735
CABP-1200	382	-	388	770
Phase 2/3 ABSSSI, cSSSI, and CABP studies (SC23)	**1252**	**869**	**388**	**2509**
ABSI-1108	323	322	-	645
ABSI-16301	368	367	-	735
CSSI-0702	111	108	-	219
CSSI-0804	68	72	-	140
CABP-1200	382	-	388	770

Source: Clinical Safety Summary Table 2 – ISS Table 14.1.1.1

Patient exposure

The mean duration for treatment in the phase 2/3 programme was comparable between treatment arms (9 days for omadacycline, 8.5 days for linezolid, 9.6 days for moxifloxacin). Similar treatment durations are observed when stratifying according to the way of application (iv/oral switch therapy in studies ABSI-1108 and CABP-1200, oral only therapy in ABSI-16301).

Table S2 Extent of exposure in the phase 2/3 program with omadacycline

Category	Omada SC23 n (%)	Omada S23 n (%)	Linezolid S23/SC23 n (%)	Omada AC3 n (%)	Omada A3 n (%)	Linezolid A3/AC3 n(%)	Moxiflox CABP (C3) n (%)
Treated (n)	1252	870	869	1073	691	689	388
Completed study (n/%)	1142 (91.2)	786 (90.3)	772 (88.8)	971 (90.5)	615 (89.0)	604 (87.7)	362 (93.3)
Prematurely discontinued (n/%) due to	110 (8.8)	84 (9.7)	97 (11.2)	102 (9.5)	76 (11.0)	85 (12.3)	26 (6.7)
AE	9 (0.7)	2 (0.2)	3 (0.3)	8 (0.7)	1 (0.1)	1 (0.1)	9 (2.3)
Lost to follow-up	51 (4.1)	51 (5.9)	64 (7.4)	48 (4.5)	48 (6.9)	56 (8.1)	3 (0.8)
Withdrawal by subject	29 (2.3)	22 (2.5)	18 (2.1)	27 (2.5)	20 (2.9)	16 (2.3)	8 (2.1)
Physician decision	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.3)
Death c)	6 (0.5)	0	2 (0.2)	6 (0.6)	0	2 (0.3)	3 (0.8)
Other	14 (1.1)	8 (0.9)	8 (0.9)	12 (1.1)	6 (0.9)	8 (1.2)	2 (0.5)
Mean duration treatment (SD)	9.2 (2.99)	9.0 (3.02)	8.9 (3.34)	9.0 (2.87)	8.7 (2.81)	8.5 (2.96)	9.6 (2.95)
Mean duration iv therapy (SD)	5.0 (2.32)	4.4 (2.00)	4.6 (2.66)	5.0 (2.35)	4.3 (1.89)	4.4 (2.10)	5.7 (2.54)
Mean duration oral therapy (SD)	6.4 (2.59)	6.9 (2.64)	6.8 (2.79)	6.4 (2.66)	7.0 (2.74)	6.8 (2.81)	5.2 (2.04)

Source: ISS, Table 14.1.3.5.

Adverse events

In the All Studies Pool (SC23) approximately 50% of subjects reported AEs. Drug related TEAEs occurred in approximately 30% of the subjects in the ABSSSI+cSSSI Phase 2 and 3 Studies (S23 pool) vs approximately 10 % in the CABP study (C3 pool). Serious TAES and TEAEs leading to discontinuation of the treatment occurred more often in individuals treated for pneumonia compared to subjects treated for ABSSSI/cSSSI. Of note, although overall low in frequency, TEAEs leading to death are more often observed in the omadacycline arm of the CABP study compared to active comparator.

Table S5A Overview of Treatment-Emergent Adverse Events in the different safety pools

Category	**Omada SC23** N=1252 **n (%)**	**Omada S23** N=870 n (%)	**Linezolid SC23/S23** N=869 n (%)	**Omada AC3** N=1073 n (%)	**Omada A3** N=691 n (%)	**Linezolid A3** N=689 n(%)	**Moxiflox** N=388 n (%)
Subjects with any TEAE	611 (48.8)	454 (52.2)	397 (45.7)	510 (47.5)	353 (51.1)	284 (41.2)	188 (48.5)
n (%) with:							
Drug-related TEAE	301 (24.0)	262 (30.1)	185 (21.3)	236 (22.0)	197 (28.5)	111 (16.1)	69 (17.8)
Serious TEAE	43 (3.4)	20 (2.3)	16 (1.8)	39 (3.6)	16 (2.3)	13 (1.9)	26 (6.7)
Drug-related serious TEAE	2 (0.2)	0	1 (0.1)	2 (0.2)	0	1 (0.1)	2 (0.5)
TEAE leading to death	9 (0.7)	1 (0.1)	3 (0.3)	8 (0.7)	0	3 (0.4)	4 (1.0)
TEAE leading to premature discontinuation of the article	35 (2.8)	14 (1.6)	12 (1.4)	33 (3.1)	12 (1.7)	10 (1.5)	27 (7.0)
TEAE leading to dose interruption of test article	3 (0.2)	3 (0.3)	0	2 (0.2)	2 (0.3)	0	0
Serious TEAEs leading to premature discontinuation of test article	17 (1.4)	7 (0.8)	5 (0.6)	16 (1.5)	6 (0.9)	5 (0.7)	11 (2.8)

Source: Table 7 Clinical summary, ISS Table 14.3.1.1.1-5

Table S5B Overview of Treatment-Emergent Adverse Events in the CABP phase III study

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

Source: Clinical Overview, Table 15

The most common adverse events associated with omadacycline are nausea (15.3%), vomiting (8.0%), headache (4.2%), ALT increased (3.7%), AST increased (3.0%), diarrhoea (2.6%), cellulitis (2.4%), wound infection (2.4%), constipation (2.2%) and infusion site extravasation (2.2%) (SC23 pool). Elevations of ALT, AST and GGT were common observations in the S23 and C3 study pool with omadacycline. Infusion site reactions are seen in very low frequency with omadacycline.

Heart rate related TEAEs including tachycardia (0.7%, SC23 pool), atrial fibrillation (0.2%, SC23 pool) and palpitations (0.5%, SC23 pool) are seen in omadacycline treated subjects. Those events occurred in low frequency and were only slightly more often observed in the omadacycline group compared to comparator treated subjects (frequencies of 0.5%/0.1%/0%, respectively, in the Linezolid arm of the SC23 pool).

Allergic reactions (pruritus, rash) were rarely seen with omadacycline and in a comparable frequency to linezolid or moxifloxacin.

Class side effects of tetracyclines, such as phototoxicity or pseudotumor cerebri, are not observed with omadacycline. No cases of *C. difficile* were identified with omadacycline. Furthermore, lipase (and amylase) elevations are observed with omadacycline (included in the SmPC).

Table S7A. Summary of Treatment-Emergent Adverse Events (TEAEs) ≥2% by Preferred Term in the Safety Population S23 ABSSSI Pooling Group (ABSSSI+cSSSI Phase 2 and 3 Studies)

Preferred Term (PT)	Omadacycline (n=870) n (%)		Linezolid (N=869) n (%)		Risk Difference Omadacycline – Linezolid (95% CI)	
Subjects with at least one TEAE	454	(52.2)	397	(45.7)	6.7	(2.05, 11.29)
Nausea	182	(20.9)	87	(10.0)	11.0	(7.62, 14.34)
Vomiting	90	(10.3)	42	(4.8)	5.5	(3.06, 8.03)
Headache	45	(5.2)	34	(3.9)	1.3	(-0.64,3.25)
Alanine aminotransferase increased	32	(3.7)	36	(4.1)	-0.5	(-2.29,1.36)
Wound infection	30	(3.4)	23	(2.6)	0.8	(-0.81,2.40)
Aspartate aminotransferase increased	29	(3.3)	31	(3.6)	-0.2	(-1.96,1.48)
Cellulitis	29	(3.3)	26	(3.0)	0.3	(-1.29,1.99)
Diarrhoea	28	(3.2)	40	(4.6)	-1.4	(-3.17,0.47)
Infusion site extravasation	28	(3.2)	20	(2.3)	0.9	(-0.59,2.42)
Subcutaneous abscess	23	(2.6)	27	(3.1)	-0.5	(-2.03,1.09)
Blood creatine phosphokinase increased	19	(2.2)	9	(1.0)	1.2	(-0.01,2.35)
Constipation	18	(2.1)	9	(1.0)	1.0	(-0.11,2.20)
Dizziness	18	(2.1)	17	(2.0)	0.1	(-1.16,1.44)

Source: ISS Table 14.3.1.4.2

Table S7B. Summary of Treatment-Emergent Adverse Events (TEAEs) ≥2% by Preferred Term in the Safety Population C3 CABP (Phase 3 Study)

PT	Omadacycline N = 382 n (%)	Moxifloxacin N = 388 n (%)	Risk Difference Omada - Moxifloxacin (95% CI)
Subjects with at least one TEAE	157 (41.1)	188 (48.5)	-7.4 (-14.36, -0.35)
ALT increased	14 (3.7)	18 (4.6)	-1.0 (-3.79, 1.84)
GGT increased	13 (3.4)	11 (2.8)	0.6 (-1.89, 3.02)
Insomnia	10 (2.6)	8 (2.1)	0.6 (-1.58, 2.69)
Vomiting	10 (2.6)	8 (2.1)	0.6 (-1.58, 2.69)
Constipation	9 (2.4)	6 (1.5)	1.1 (-0.95, 2.09)
Nausea	9 (2.4)	21 (5.4)	0.8 (-1.15, 2.76)
AST increased	8 (2.1)	14 (3.6)	-3.1 (-5.77, -0.34)
Headache	7 (1.8)	3 (0.8)	-1.5 (-3.86, 0.83)
Anaemia	7 (1.8)	3 (0.8)	0.8 (-1.02, 2.63)

Source: ISS Table 14.3.1.4.3

In the phase 1 studies nausea, vomiting, diarrhoea and ALAT increased were primarily observed. Furthermore transient dose-dependent increases of HR were seen in relation with omadacycline with resolved within 6 hours.

AE by severity

Mild and moderate TEAEs occurred slightly more often in the omadacycline arm of the ABSSSI studies (32.3% omadacycline, 26.0% linezolid and 17.1% omadacycline, 12.8% linezolid). Moderate TEAEs

occurred less often in omadacycline treated subjects compared to moxifloxacin in the CABP study (11.0% omadacycline, 17.0% moxifloxacin). Severe TEAEs were equally distributed between test drug and control arm in the ABSSSI studies (1.7% of subjects in the omadacycline group and 2.5% of subjects in the linezolid group) and the CABP study (6.5% of subjects in the omadacycline group and 6.7% of subjects in the moxifloxacin group).

Drug related TEAEs

The most frequently reported drug-related TEAEs in the A3 ABSSSI Pooling Group (ABSSSI Phase 3 Studies) in the omadacycline arm were nausea (18.5%) and vomiting (9.6%), ALT increased (3.2%), AST increased (2.7%) and diarrhoea (2.3%).

In the ABSSSI Phase 3 studies, the frequency of drug-related TEAEs in the omadacycline group was higher (28.5%) compared to the omadacycline group in Study PTK0796-CABP-1200 (10.2%). The most frequently reported drug-related TEAEs (≥ 1% for any group) by PT that occurred at a higher percentage (≥ 1% difference) in the omadacycline group were nausea (1.8% CABP, 18.5% ABSSSI) and vomiting (0% CABP, 9.6% ABSSSI). All other drug-related TEAEs (≥ 1% for any group) were similar between treatment groups for both indications. The higher drug related TEAEs for the C3 safety pool was due to greater drug-related nausea and vomiting in the PTK0796 ABSI-16301 study. Furthermore rates of liver enzyme elevations were also higher in the A3 pool compared to CABP (ALT 3.2% vs 1.8%; AST: 2.7% vs. 1.3%)

AEs by route of administration

Nausea and vomiting occur more often in cases where omadacycline is given po rather than iv. Gastrointestinal events are known and generally manageable tetracycline class effects. Based on the food interaction PK studies revealing decreased exposure to omadacycline when administered following a meal the Applicant proposed the administration of this medicinal product under fasting condition which is agreed. The proposed precaution and listed AEs related to the gastrointestinal disorders in SmPC are considered sufficient at this time. Finally, the Applicant claims that the impact of a light meal on the tolerability is currently evaluated and therefore is asked to provide such safety data (LoQI).

Table S9. Number (%) of Subjects With the Most Frequent TEAEs (≥ 2% for Any Group) Overall and by PT (Studies ABSI-1108 and CABP-1200)

	Omadacycline			Linezolid			Moxifloxacin		
PT	iv N = 705 n (%)	po N = 581 n (%)	Overall N = 705 n (%)	iv N = 322 n (%)	po N = 283 n (%)	Overall N = 322 n (%)	iv N = 388 n (%)	po N = 294 n (%)	Overall N = 388 n (%)
Subjects with at least 1 TEAE	226 (32.1)	165 (28.4)	313 (44.4)	100 (31.1)	77 (27.2)	147 (45.7)	143 (36.9)	74 (25.2)	188 (48.5)
Infusion site extravasation	28 (4.0)	0	28 (4.0)	19 (5.9)	0	19 (5.9)	0	0	0
Nausea	16 (2.3)	33 (5.7)	49 (7.0)	22 (6.8)	11 (3.9)	32 (9.9)	10 (2.6)	11 (3.7)	21 (5.4)
Hypertension	15 (2.1)	5 (0.9)	19 (2.7)	3 (0.9)	2 (0.7)	4 (1.2)	8 (2.1)	3 (1.0)	11 (2.8)
ALT increased	13 (1.8)	10 (1.7)	23 (3.3)	1 (0.3)	13 (4.6)	14 (4.3)	17 (4.4)	1 (0.3)	18 (4.6)
Headache	12 (1.7)	7 (1.2)	18 (2.6)	8 (2.5)	5 (1.8)	13 (4.0)	5 (1.3)	0	5 (1.3)
Vomiting	11 (1.6)	16 (2.8)	27 (3.8)	12 (3.7)	6 (2.1)	16 (5.0)	2 (0.5)	5 (1.7)	6 (1.5)
AST increased	10 (1.4)	6 (1.0)	16 (2.3)	3 (0.9)	10 (3.5)	12 (3.7)	13 (3.4)	1 (0.3)	14 (3.6)
Insomnia	8 (1.1)	5 (0.9)	13 (1.8)	4 (1.2)	0	4 (1.2)	8 (2.1)	0	8 (2.1)
Subcutaneous abscess	8 (1.1)	10 (1.7)	17 (2.4)	14 (4.3)	5 (1.8)	19 (5.9)	0	0	0
Cellulitis	6 (0.9)	10 (1.7)	16 (2.3)	5 (1.6)	10 (3.5)	15 (4.7)	0	0	0
Diarrhoea	6 (0.9)	6 (1.0)	11 (1.6)	5 (1.6)	5 (1.8)	10 (3.1)	18 (4.6)	14 (4.8)	31 (8.0)

Source: ISS Tables 14.3.1.9.1.1 and Table 14.3.1.9.1.2

Table S10. Number (%) of Subjects With the Most Frequent TEAEs (≥ 2% for Any Group) Overall and by PT (Study ABSI-16301 (oral only administration))

Body System	Omadacycline (N = 368) n (%)	Linezolid (N = 367) n (%)
Subjects with at least 1 TEAE	197 (53.5)	137 (37.3)
Nausea	111 (30.2)	28 (7.6)
Vomiting	62 (16.8)	11 (3.0)
Wound infection	22 (6.0)	17 (4.6)
ALT increased	19 (5.2)	11 (3.0)
AST increased	17 (4.6)	12 (3.3)
Diarrhoea	15 (4.1)	10 (2.7)
Headache	13 (3.5)	8 (2.2)
Cellulitis	12 (3.3)	9 (2.5)
Abdominal pain upper	10 (2.7)	4 (1.1)
Subcutaneous abscess	6 (1.6)	8 (2.2)

Source: Study ABSI-16301, Table 14.3.1.1.2.1

AEs of special interest

1. Hepatic events

Liver enzyme and bilirubin elevations are typical class effects of tetracyclines and were expected to be seen. Elevations of AST, ALT, GGT and Bilirubin were observed with omadacycline. The frequencies of these events were roughly comparable with frequencies seen in the comparator arms in the different study pools. The great majority of these events were mild in intensity. Only in one case, where omadacycline was evaluated as causative for liver enzyme elevations, the treatment with the test drug had to be discontinued. No cases of liver failure or cases fulfilling Hy´s law were detected as being caused by omadacycline. The Applicant has included elevations of GGT, AST, ALT (common) and bilirubin and ALP (uncommon) in the SmPC.

Table S13. Summary of Hepatic Events of Interest by PT (AC3 Pool)

Category PT	Omadacycline N = 1073 n (%)	Linezolid N = 689 n (%)	Moxifloxacin N = 388 n (%)
Liver-related investigations, signs, and symptoms	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 system-related investigations, signs, and symptoms	7 (0.7)	2 (0.3)	6 (1.5)
Blood bilirubin increased	5 (0.5)	1 (0.1)	3 (0.8)
Blood ALP increased	3 (0.3)	1 (0.1)	4 (1.0)

Source: ISS Table 14.3.1.12.4.

2. Gastrointestinal Events

Nausea and vomiting were the most abundant side effects with omadacycline, and occurred especially during the oral application of the drug. The events were of mild or moderate intensity.

The applicant has included nausea (very common), vomiting (common), diarrhoea (common) in the SmPC, which is endorsed. Other GI events that have been observed with omadacycline include constipation (2.1%), abdominal pain (1.3%, included in the SmPC as common), and dyspepsia (0.8%, included in the SmPC as uncommon) which occurred in similar frequencies as with the comparator.

Table S14. Summary of GI Events of Interest by PT (AC3 Pool)

PT	Omadacycline N = 1073 n (%)	Linezolid N = 689 n (%)	Moxifloxacin N = 388 n (%)
Nausea	160 (14.9)	60 (8.7)	21 (5.4)
Vomiting	89 (8.3)	27 (3.9)	6 (1.5)
Diarrhoea	26 (2.4)	20 (2.9)	31 (8.0)
Constipation	16 (1.5)	5 (0.7)	6 (1.5)
Abdominal pain upper	15 (1.4)	6 (0.9)	2 (0.5)
Abdominal pain	9 (0.8)	5 (0.7)	2 (0.5)
Dyspepsia	7 (0.7)	7 (1.0)	2 (0.5)
Dry mouth	3 (0.3)	6 (0.9)	0
Toothache	3 (0.3)	0	0

Pooling group AC3 includes: Studies ABSI-1108, ABSI-16301, and CABP-1200. PT, for each PT term;
Source: Summary of clinical safety, Table 40

3. Heart Rate and Cardiac events

The frequency of subjects with at least 1 TEAE within the Cardiac disorders SOC in the pooled AC3 pool, were highest in the moxifloxacin group (5.2%), followed by 2.1% in the omadacycline group and 0.4% in the linezolid group. The Applicant has investigated HR and cardiac events of interest by PT (see Table S15). Only slight numeric differences are observed for PTs belonging to the category cardiac arrest and tachyarrhythmias in the CABP study (C3 pool, table below, updated/completed table to be found in the answer to question 233). The Applicant has given a detailed description on cerebrovascular events in the different study pools compared to comparator arm. That is: 3 subjects had a cerebrovascular event in the omadacycline arm, 2 in the CABP study (discussed in question 230), in the A3 pool and 1 event of transient dysarthria together with transient hemiparesis was detected in the phase 2 ABSSSI studies. These events were probably a result of transient progression of Parkinson's disease (discussed in question 230). No event was detected in the comparator arms, leading to a slightly higher overall frequency of 2/vs 0/ in the SC3 pool. Those two cases are characterised by older subjects with underlying cardiovascular multi-morbidity, which predisposed to the strokes the occurred under study run. A clear causative relation to study drug treatment can therefore not be drawn.

Table S15. Summary of HR and Cardiac Events of Interest by PT (A3 and C3 Pool)

	A3 (ABSSSI)		C3 (CABP)		
Category PT	Omadacycline N = 691 n (%)	Linezolid N = 689 n (%)	Omadacycline N = 382 n (%)	Moxifloxacin N = 388 n (%)	Risk Difference Omada (CABP)-Moxi (95%)
Cardiac arrest	**0**	**1 (0.1)**	**4 (1.0)**	**1 (0.3)**	**0.8 (-0.35, 1.93)**
Cardiogenic shock		1 (0.1)	2 (0.5)	1 (0.3)	
Cardiac arrest		ng	1 (0.3)	0	
Cardio-respiratory arrest		ng	1 (0.3)	0	
Cardiac failure	**0**	**2 (0.3)**	**6 (1.6)**	**5 (1.3)**	**0.3 (-1.4, 1.96)**
Cardiac failure		1 (0.1)	3 (0.8)	3 (0.8)	
Cardiogenic shock		1 (0.1)	2 (0.5)	1 (0.3)	
Acute pulmonary edema		ng	1 (0.3)	0	
Cardiac failure congestive		ng	0	1 (0.3)	
Hepatic congestion		ng	0	1 (0.3)	
Right ventricular failure		ng	0	1 (0.3)	
Ischemic heart disease	**0**	**1 (0.1)**	**3 (0.8)**	**4 (1.0)**	**-0.2 (-1.58, 1.09)**

Table S15. Summary of HR and Cardiac Events of Interest by PT (A3 and C3 Pool)

	A3 (ABSSSI)		C3 (CABP)		
Category PT	**Omadacycline N = 691 n (%)**	**Linezolid N = 689 n (%)**	**Omadacycline N = 382 n (%)**	**Moxifloxacin N = 388 n (%)**	**Risk Difference Omada (CABP)-Moxi (95%)**
Acute myocardial infarction		ng	2 (0.5)	0	
Myocardial ischemia		1 (0.1)	1 (0.3)	2 (0.5)	
Angina pectoris		ng	0	2 (0.5)	
Tachiarrhythmias	**3 (0.4)**	**0**	**3 (0.8)**	**1 (0.3)**	**0.5 (-0.49, 1.55)**
Atrial fibrillation	2 (0.3)	0	3 (0.8)	1 (0.3)	
Atrial flutter	Ng	ng	1 (0.3)	0	
Sinus tachycardia	1 (0.1)	0	Ng	ng	

ng = value not displayed in the ISS table
Source: ISS Table 14.3.1.12.1. and 14.3.1.12.3.

The applicant has added a 3 endpoint MACE analysis for both the AC3 and the SC23 pool. Results confirm preliminary observations of numeric imbalances for the events cerebrovascular events and cardiac infarction events on an overall low frequency level and show balanced counts in cardiac induced deaths. Events occurred in patients often showing several cardiovascular risk factors. Numerical imbalances for MI almost disappear when additionally taking cases of elevated CPK into account (1.2% (O) vs 0.9% (L) vs 1.0% (M), AC3 group). At this stage, MACE analysis does not provide further explanation for imbalances in mortality seen with omadacycline.

Post-hoc table 1: Summary of Cerebrovascular, Myocardial Infarction Treatment-Emergent Adverse Events (TEAEs), and Cardiac Deaths AC3 Pooling Group (ABSSSI+CABP Phase 3 Studies) – Safety Population

	Omadacycline (N=1073) n (%)	Linezolid (N=689) n (%)	Moxifloxacin (N=388) n (%)
Number of subjects with at least one event	7 (0.7)	2 (0.3)	1 (0.3)
Subjects with at least one cerebrovascular TEAE	3 (0.3)	0	0
Subjects with at least one myocardial infarction TEAE	3 (0.3)	0	0
Cardiac Disorders SOC Deaths	3 (0.3)	2 (0.3)	1 (0.3)

Source: Table 61.7
Pooling group AC3 includes: ABSI-1108, ABSI-16301, CABP-1200.
Coding of Preferred Term based on MedDRA Version 17.1.
Cerebrovascular TEAEs are based on Cerebrovascular Disorders Standardized MedDRA Query (SMQ).
Myocardial infarction TEAEs are based on Myocardial Infarction Standardized MedDRA Query (SMQ) excluding Blood Creatine Phosphokinase Increased preferred term.

4. Tetracycline Class Related Events

- 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
- fungal infections, in particular vulvovaginal fungal infections.
- Pill esophagitis is noted with tetracyclines, in particular doxycycline

Table S16. Summary of Tetracycline Class Events of Interest by PT (AC3 Pool)

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
Fungal infections	11 (1.0)	6 (0.9)	5 (1.3)
Oral candidiasis	5 (0.5)	1 (0.1)	1 (0.3)
Vulvovaginal mycotic infection	3 (0.3)	5 (0.7)	0
Fungal skin infection	1 (0.1)	0	0
Oesophageal candidiasis	1 (0.1)	0	1 (0.3)
Vulvovaginal candidiasis	1 (0.1)	0	0
Oral fungal infection	0	0	1 (0.3)
Respiratory moniliasis	0	0	2 (0.5)
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
Oesophageal 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)

Pooling group AC3 includes: Studies ABSI-1108, ABSI-16301, and CABP-1200.

Source: ISS Table 14.3.1.12.4.

- Anti-anabolic events as represented by blood urea nitrogen (BUN) increased and azotemia

The TEAE of blood urea increased occurred in 1 (0.1%) omadacycline subject in the AC3 pool (Subject 1200-555 5003; mild, unrelated to test article, resolved) and no linezolid or moxifloxacin subject.

- Central nervous system side effects including light-headedness, vertigo or dizziness

Vertigo and dizziness occurred in < 2% of subjects and were comparable between treatment groups

- Hypersensitivity

Hypersensitivity reactions occurred in 1.9% of omadacycline subjects, 1.7% of linezolid subjects, and 2.6% of moxifloxacin subjects, none of them serious in the omadacycline arm.

A total of 9 subjects (1 omadacycline, 4 linezolid, 4 moxifloxacin) had a hypersensitivity event that led to test article discontinuation. Pruritus and rash have been included in the SmPC as uncommon events under "skin reactions". hypersensitivity reaction has been included in the SmPC (uncommon), which is in principal endorsed.

In the pivotal phase 3 trials (AC3 pool) the preferred term "erythema" was uncommon; treatment emergent adverse events of infusion site erythema, application site erythema, and penile erythema were not included in determining the frequency of this adverse event. "Erythema" occurred in 6 (0.6%)

of OMC patients, 3 (0.4% linezolid patients, and in 0 moxifloxacin patients. In only 1 omadacycline patient was the erythema considered related to the study drug however the number of cases was double in the omadacycline treatment group relative to the comparators and skin reactions are plausible and not infrequent following antibiotic administration. The Applicant has suggested including Erythema as an uncommon ADR in the SmPC, which is endorsed

- Photosensitivity

No omadacycline subjects reported photosensitivity. Study subjects had a certain amount of sun exposure as studies were run in sun-rich areas such as e.g. California. Photosensitivity has been included as a warning in the SmPC (class effect), which is endorsed.

- Pancreatitis

One subject (Subject 1200-373-5004) in the omadacycline group had a TEAE of chronic pancreatitis on Day 5 that was considered mild in severity and not related to test article. No action was taken with test article and the event was considered ongoing.

- Fungal infections, in particular vulvovaginal fungal infections

The incidence of fungal infections was low, occurring in 11 (1.0%) omadacycline subjects, 6 (0.9%) linezolid subjects, and 5 (1.3%) moxifloxacin subjects. These events were considered mild or moderate in severity and did not lead to test article discontinuation or dose interruption.

- Pill esophagitis is noted with tetracyclines, in particular doxycycline

Esophagitis was reported in only 1 (0.1%) omadacycline subject (Subject 1200-414-5001) during iv treatment. The event was mild, not related, and resolved. Oesophageal ulceration was not reported.

- *C. difficile* infection

C. difficile infection cases occurred only in the moxifloxacin group (2.1%).

Serious adverse events and deaths

An imbalance in the mortality rate is noted in the CABP study between omadacycline (2.1%) and moxifloxacin (1.0%) (95% CI -0.7 to 2.8). The point estimate for the omadacycline and moxifloxacin arms in CABP-1200 study is within the reported range of other CAP/CAPB studies, however this is not entirely reassuring, as the very reason for a randomised comparator arm is to calibrate the experiment and provide a reference for the numerical findings in the experimental arm. Overall, there were 17 deaths (10 omadacycline, 3 linezolid, 4 moxifloxacin) reported in the five Phase 2 and 3 studies. Across the omadacycline clinical development programme, there were 10 (0.8%) omadacycline and 7 (0.6%) comparator subjects who died. Among the comparator deaths, 4 (1.0%) occurred on moxifloxacin and 3 (0.4%) occurred on linezolid.

Table S17. Listing of Deaths

Subject ID	Age/ Gender	Study Medication	PT	Last Study Medication (Study Day)	Date of Death (Study Day)	Relationship to Study Medication (study physician)
Study CSSI-0804						
804-811-4135	51/M	Omadacycline	Pleural effusion	25-MAR-2010 (Day 10)	19-APR-2010 (Day 35)	Not related
			Lung cancer metastatic	25-MAR-2010 (Day 10)	19-APR-2010 (Day 35)	Not related
Study ABSI-1108						
1108-262-0035	60/M	Omadacycline	Overdose	07-AUG-2015 (Day 1)	08-AUG-2015 (Day 2)	Not related

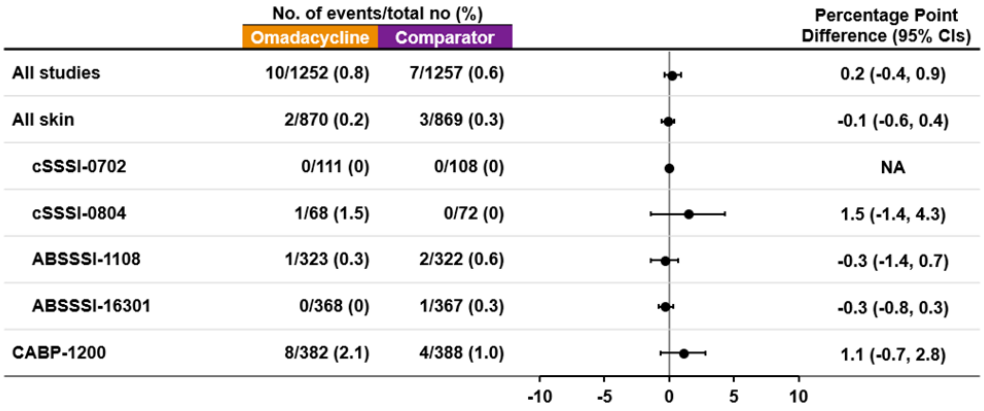
Table S17. Listing of Deaths

Subject ID	Age/ Gender	Study Medication	PT	Last Study Medication (Study Day)	Date of Death (Study Day)	Relationship to Study Medication (study physician)
1108-124-0005	88/M	Linezolid	Cardiac failure	21-MAR-2016 (Day 7)	26-MAR-2016 (Day 12)	Not related
1108-253-0018	43/M	Linezolid	Cardiac arrest	16-JAN-2016 (Day 7)	18-JAN-2016 (Day 9)	Not related
Study ABSI-16301						
16301-604-3056	62/F	Linezolid	Death	10-JAN-2017 (Day 10)	APR-2017 (unknown)	Not related
Study CABP-1200						
1200-241-5019	68/M	Omadacycline	Cerebrovascular accident	25-OCT-2016 (Day 7)	31-OCT-2016 (Day 13)	Not related
1200-244-5008	72/M	Omadacycline	Aortic aneurysm rupture	28-AUG-2016 (Day 8)	29-AUG-2016 (Day 9)	Not related
1200-311-5005	67/M	Omadacycline	Septic shock	01-FEB-2016 (Day 1)	02-FEB-2016 (Day 2)	Related
1200-334-5001	86/F	Omadacycline	Pneumonia	22-JAN-2016 (Day 9)	12-FEB-2016 (Day 30)	Not related
			Acute respiratory distress syndrome	22-JAN-2016 (Day 9)	12-FEB-2016 (Day 30)	Not related
1200-343-5001	90/F	Omadacycline	Cardiogenic shock	13-APR-2016 (Day 13)	20-APR-2016 (Day 20)	Not related
1200-405-5015	76/M	Omadacycline	Cardio-respiratory arrest	21-FEB-2016 (Day 2)	21-FEB-2016 (Day 2)	Related
1200-411-5003	74/F	Omadacycline	Acute respiratory failure	05-DEC-2016 (Day 4)	26-DEC-2016 (Day 25)	Not related
			Multi-organ failure	05-DEC-2016 (Day 4)	26-DEC-2016 (Day 25)	Not related
1200-551-5007	66/M	Omadacycline	Acute myocardial infarction	16-OCT-2016 (Day 2)	16-OCT-2016 (Day 2)	Not related
1200-307-5006	83/M	Moxifloxacin	Cardiac failure	31-DEC-2015 (Day 9)	31-DEC-2015 (Day 9)	Not related
1200-334-5005	85/F	Moxifloxacin	Acute respiratory failure	28-APR-2016 (Day 3)	04-MAY-2016 (Day 9)	Not related
1200-354-5001	82/M	Moxifloxacin	Lung neoplasm	05-DEC-2016 (Day 14)	11-DEC-2016 (Day 20)	Not related
1200-355-5003	72/F	Moxifloxacin	Pancreatic carcinoma	24-NOV-2016 (Day 8)	26-JAN-2017 (Day 71)	Not related

Source: ISS Listing 16.2.7.3.

Mortality

Figure 7. Forest Plot of Mortality in the SC23 Pool



Source: Clinical Overview, Figure 1

Mortality in ABSSSI

In all Phase 2 and 3 studies of skin infections (S23 Pool), the mortality rate was 0.2% for omadacycline versus 0.3% for linezolid (Figure 7).

Mortality in CABP

The demographic and baseline factors for the omadacycline and moxifloxacin-treated subjects who died generally describe a subject with CABP and an elevated moderate risk of mortality (age over 65 years, PORT Risk Class IV, with underlying cardiovascular and pulmonary comorbidities); 6 of 8 omadacycline subjects who died, and 2 of 4 moxifloxacin subjects who died, were PORT Risk Class IV.

To determine if there was a numerical trend for specific mortality-associated TEAEs (TEAEs with the outcome of death) that could represent a potential biologically plausible relationship to treatment, "mortality-associated TEAEs by PTs" were examined amongst subjects who survived Study CABP-1200.

Table S18 Summary of Mortality-associated TEAEs by PT in Subjects Who Did Not Die in Study CABP-1200 (C3 Pool, Safety Population)

PT	Omadacycline (N = 374)	Moxifloxacin (N = 384)
Acute myocardial infarction	1	0
Cardiogenic shock	1	1
Cardiac failure	3	2
Cardio-respiratory arrest	0	0
Pneumonia	3	7
Septic shock	0	2
Acute respiratory distress syndrome	1	0
Acute respiratory failure	1	2
Aortic aneurysm rupture	0	0
Multi-organ failure	0	0
Cerebrovascular accident	1	0
Lung neoplasm	7	2
Pancreatic carcinoma	0	0

Source: Clinical Overview, Appendix, Table 21

Similar numbers of events were observed between the omadacycline and moxifloxacin groups for all of the mortality associated TEAE PTs, including terms related to myocardial ischemia, heart failure, and progression of pneumonia, including respiratory failure.

An additional analysis was conducted to determine if the omadacycline subjects who died in Study CABP 1200 had significant changes in HR. Changes in HR for subjects who died were of small magnitude (< 10 bpm) and well within the observed population based median values for HR change in subjects treated with either omadacycline (who survived) or moxifloxacin (who survived or died). QT interval corrected for HR using Fridericia's formula (QTcF) was not increased in omadacycline subjects across the ABSSSI and CABP populations studied (SCS, Table 30). No imbalances were seen between treatment arms in cardiac TEAE (myocardial infarction, myocardial ischemia, heart failure, and tachyarrhythmias) in Study CABP 1200 (ISS, Table 14.3.1.12.3, TEAEs of interest, Safety table S15) or across the integrated safety database (SCS, Table 20).

Since a lack of efficacy could result in increased mortality, additional analyses were conducted to determine whether efficacy was decreased in important subgroups: 1) higher probability of mortality (eg, PORT Risk Class); 2) higher severity (eg, SMART-COP); 3) subjects meeting sepsis criteria, and 4) baseline bacteraemia). The results of these subgroup population analyses demonstrated similar efficacy between omadacycline and moxifloxacin.

To assess whether early failure to either antibiotic therapy could result in the observed numerical difference in mortality, achievement of early clinical stability criteria was analysed in the omadacycline and moxifloxacin treatment groups. These data demonstrated a high and similar percentage of subjects in both treatment groups (89%) who successfully achieved early clinical stability, as defined by meeting all 5 of the stabilization criteria and did not vary appreciably between PORT Risk Class III and IV. The high percentages are consistent with the high level of efficacy observed at the ECR assessment.

Finally, inspection of individual microbiology data revealed no pathogen consistently associated with the progression of the incident pneumonia to death.

Serious AEs

The incidence of SAEs was overall low in the omadacycline and the comparator arms. A systematic occurrence of a specific type of SAEs is not observed in the omadacycline group.

3 cases of cerebrovascular accidents/hemiparesis plus dysarthria were observed in the omadacycline group in the SC23 pool. Scrutiny of submitted narratives allowed the conclusion that those events are not clearly associated with study drug treatment (1 case of Parkinson's disease and strokes in two older subjects with underlying cardiovascular-morbidity)

Table S21 Patients with at least one serious TEAE – SC23 safety pool

System Organ Class (SOC) Preferred Term (PT)	Omada (N=1252) n (%)	Linezolid (N=869) n (%)	Moxifloxacin (N=388) n (%)
Subjects with at Least One Serious TEAE	43 (3.4)	16 (1.8)	26 (6.7)
Cardiac disorders	5(0.4)	2 (0.2)	2(0.5)
Acute myocardial infarction	2(0.2)	0	0
Cardiogenic shock	2(0.2)	0	1(0.3)
Cardiac arrest	1(0.1)	1 (0.1)	0
Cardiac failure	1(0.1)	1 (0.1)	1(0.3)
Cardio-respiratory arrest	1(0.1)	0	0
Tachycardia	1(0.1)	0	0
Pericardial effusion	0	0	1(0.3)
Right ventricular failure	0	0	1(0.3)
Gastrointestinal disorders	1(0.1)	0	1(0.3)
Small intestinal obstruction	1(0.1)	0	0
Colitis	0	0	1(0.3)

General disorders and administration site conditions	3(0.2)	1 (0.1)	0
Drug withdrawal syndrome	1(0.1)	0	0
Multi-organ failure	1(0.1)	0	0
Non-cardiac chest pain	1(0.1)	0	0
Death	0	1 (0.1)	0
Hepatobiliary disorders	3(0.2)	0	1(0.3)
Cholecystitis acute	2(0.2)	0	0
Hepatic failure	1(0.1)	0	0
Hepatic congestion	0	0	1(0.3)
Infections and infestations	21(1.7)	8 (0.9)	16(4.1)
Cellulitis	3(0.2)	3 (0.3)	0
Influenza	3(0.2)	0	0
Subcutaneous abscess	3(0.2)	0	0
Wound infection	3(0.2)	2 (0.2)	0
Pneumonia	2(0.2)	0	6(1.5)
Bacteraemia	1 (0.1)	0	0
Gastroenteritis	1 (0.1)	0	0
Gastroenteritis rotavirus	1 (0.1)	0	0
Hepatitis C	1 (0.1)	0	0
Infectious pleural effusion	1 (0.1)	0	1(0.3)
Septic shock	1 (0.1)	0	2(0.5)
Staphylococcal bacteraemia	1 (0.1)	0	0
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)
Sepsis	0	3 (0.3)	0
Skin infection	0	1 (0.1)	0
Injury, poisoning and procedural complications	2(0.2)	1 (0.1)	1 (0.3)
Joint dislocation	1(0.1)	0	0
Overdose	1(0.1)	1 (0.1)	0
Bladder injury	0	0	1(0.3)
Metabolism and nutrition disorders	1(0.1)	0	0
Decreased appetite	1(0.1)	0	0
Musculoskeletal and connective tissue disorders	1(0.1)	0	0
Back pain	1(0.1)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3(0.2)	0	6 (1.5)
Lung neoplasm	2(0.2)	0	2 (0.5)
Lung neoplasm	2 (0.2)	0	2 (0.5)
Lung cancer metastatic	1(0.1)	0	0
Adenocarcinoma	0	0	11 (0.3)
Chronic lymphocytic leukaemia	0	0	1 (0.3)
Colon cancer metastatic	0	0	1 (0.3)
Pancreatic carcinoma	0	0	1 (0.3)
Nervous system disorders	3(0.2)	0	0
Cerebrovascular accident	2(0.2)	0	0
Hemiparesis	1(0.1)	0	0
Psychiatric disorders	3(0.2)	1 (0.1)	0
Anxiety	1(0.1)	0	0
Confusional state	1(0.1)	0	0
Depression	1(0.1)	0	0
Drug abuse	0	1 (0.1)	0
Renal and urinary disorders	0	0	2 (0.5)
Renal failure acute	0	0	2 (0.5)

Respiratory, thoracic and mediastinal disorders	9(0.7)	2 (0.2)	3 (0.8)
Acute respiratory failure	3(0.2)	0	3 (0.8)
Pleural effusion	3(0.2)	0	0
Acute respiratory distress syndrome distress syndrome	2(0.2)	0	0
Acute pulmonary oedema	1(0.1)	0	0
Chronic obstructive pulmonary disease	0	1 (0.1)	0
Pulmonary embolism	0	1 (0.1)	0
Skin and subcutaneous tissue disorders tissue disorders	0	1 (0.1)	0
Angioedema	0	1 (0.1)	0
Vascular disorders	1(0.1)	0	1 (0.3)
Aortic aneurysm rupture	1(0.1)	0	0
Peripheral ischemia	0	0	1 (0.3)

Source: ISS Table 14.3.1.7.5

Laboratory findings

Haematology

In general, no clinically meaningful changes from baseline were observed which were related in a negative way to omadacycline treatment. Leukocyte and neutrophil counts, which decreased after baseline in both treatment groups, and platelets which increased after baseline in the omadacycline and moxifloxacin treatment groups are consistent with clinical improvement during treatment. However, in several cases lower neutrophil counts were observed with omadacycline (>1% with a >= 2 Grade decrease). Five omadacycline subjects had neutrophil counts below 0.5. Adverse events associated with infection were limited to a single case. Cases of neutropenia were partly caused of underlying infection, in one case abundant at baseline, very short/ transient of nature and occurred in two cases at PTE. No clear association with treatment can be drawn.

The investigator reported 1% of cases of anaemia as TEAE in omadacycline subjects. The Applicant has included anaemia as common event in the SmPC. Thrombocytes did not decrease significantly in omadacycline treated subjects and suggested including thrombocytosis as an uncommon event in the SmPC. As requested, the Applicant further analysed the frequency of thrombocytosis in the AC3 pool. Data presented demonstrate that 1% of cases show at least one event of moderate platelet increase under treatment with omadacycline. The frequency is higher compared to linezolid (0.1%) and lower compared to moxifloxacin (2.1%). It is noted, the moxifloxacin lists thrombocythemia as a common occurring event in the ADR list section 4.8. Furthermore, a clear treatment to event relationship regarding shifts in platelet counts is seen with omadacycline in four cases experiencing a TEAE of thrombocytosis. Therefore, it is suggested to include thrombocytosis as often occurring event in the ADR list, section 4.8 of the SmPC.

Table S22 Summary of TEAEs by SOC and PT in the Phase 3 ABSSSI and CABP Studies (AC3 Pool)

SOC PT	Omadacycline (N = 1073) n (%)	Linezolid (N = 689) n (%)	Moxifloxacin (N = 388) n (%)
Subjects with at Least 1 TEAE	510 (47.5)	284 (41.2)	188 (48.5)
Blood and lymphatic system disorders	20 (1.9)	11 (1.6)	7 (1.8)
Anaemia	12 (1.1)	4 (0.6)	3 (0.8)
Thrombocytosis	4 (0.4)	1 (0.1)	0

Source: Summary Table 40

Clinical Chemistry

Meaningful changes of lipase (5.9%) and amylase (2.1%) are seen with omadacycline. Frequencies are roughly comparable with those seen with linezolid or moxifloxacin. No case of pancreatitis was observed with omadacycline. The applicant has included lipase elevations as uncommon event in the SmPC. Urea nitrogen elevations (class effect of tetracyclines, 4 cases showing a shift ≥ 2 in the omadacycline arm of the SC23 pool) and creatinine elevations have been rarely observed with omadacycline and were comparable to the rate seen with comparator treatment. No significant shifts in electrolytes are observed with omadacycline.

Table S23. Chemistry Results: Subjects With Incidence of at Least 2 Grade Change From Baseline (AC3 Pool)

	Omadacycline N = 1073		Linezolid N = 689		Moxifloxacin N = 388	
Subjects With at Least a 2 Grade Change From Baseline in:	**n (%)**	**Number of Subjects With a Grade 2 or Less at Baseline**	**n (%)**	**Number of Subjects With a Grade 2 or Less at Baseline**	**n (%)**	**Number of Subjects With a Grade 2 or Less at Baseline**
Renal	4 (0.4)	1049	3 (0.5)	666	5 (1.3)	382
Urea nitrogen	1 (0.1)	1042	0	663	2 (0.5)	380
Creatinine	4 (0.4)	1049	3 (0.5)	666	5 (1.3)	382
Liver	65 (6.2)	1049	42 (6.3)	666	41 (10.7)	382
ALP	2 (0.2)	1039	1 (0.2)	663	3 (0.8)	377
ALT	41 (3.9)	1049	24 (3.6)	665	21 (5.5)	381
AST	32 (3.1)	1049	24 (3.6)	665	16 (4.2)	381
GGT	25 (2.5)	1019	15 (2.3)	653	18 (4.9)	366
Total bilirubin	7 (0.7)	1047	2 (0.3)	666	6 (1.6)	381
Electrolytes	25 (2.4)	1044	16 (2.4)	665	23 (6.0)	381
Calcium hypocalcaemia (corrected for albumin)	1 (0.1)	1039	0	663	3 (0.8)	377
Calcium hypercalcaemia (corrected for albumin)	0	1038	0	663	0	377
Magnesium (hypomagnesaemia)	5 (0.5)	1041	4 (0.6)	664	2 (0.5)	380
Potassium (hypokalaemia)	2 (0.2)	1034	2 (0.3)	651	8 (2.1)	376
Potassium (hyperkalaemia)	8 (0.8)	1034	2 (0.3)	651	8 (2.1)	376
Sodium (hyponatraemia)	4 (0.4)	1041	5 (0.8)	662	2 (0.5)	377
Sodium (hypernatraemia)	7 (0.7)	1041	3 (0.5)	662	6 (1.6)	377
Other	149 (14.3)	1043	77 (11.6)	665	63 (16.5)	381
Amylase	22 (2.1)	1037	9 (1.4)	659	6 (1.6)	377
Blood glucose (Hypoglycaemia)	11 (1.1)	1036	7 (1.1)	655	3 (0.8)	377
Blood glucose (hyperglycaemia)	55 (5.5)	1003	29 (4.6)	635	20 (5.7)	353
Lipase	61 (5.9)	1037	27 (4.1)	658	22 (5.8)	379
Phosphate (hypophosphatemia)	14 (1.4)	1026	12 (1.8)	654	19 (5.1)	374
Uric Acid (hyperuricaemia)	8 (0.8)	1036	2 (0.3)	661	8 (2.1)	378

Pooling group AC3 includes: Studies ABSI-1108, ABSI-16301, and CABP-1200.
Source: ISS Table 14.3.3.6.4.

Liver values

Five omadacycline subjects (Subjects 1108-120-0004, 1200-307-5018, 16301-601-3038, 16301-604-3055, and 16301-608-3095; no subject in the comparator arms) met Hy's Law laboratory criteria assessments (defined as an ALT or AST > 3 × ULN) and total bilirubin > 2 × ULN and ALP < 2 × ULN) at any time post-Baseline in the AC3 pool. Of these, 2 (0.2%) omadacycline subjects (Subjects 16301-604-3055 and 16301-608-3095) met the Hy's law laboratory criteria assessment at the same visit post-Baseline. These patients had a medical history including concomitant medication able to induce liver enzyme elevations, ALT elevations evaluated as not related to test drug by the physician (1), drug abuse and hepatitis B infection (1), drug abuse and hepatitis C infection (2), liver

enzyme elevations already at screening (1). Taking this into consideration, the view of the Applicant that these cases do not represent drug induced liver injury seems plausible.

Changes in AST and ALT > x10 ULN occurred rarely in and were comparable between the different arms. Increases in total bilirubin and ALP were comparable between treatment groups. Increases in ALT, AST, GGT and bilirubin have been included in the SmPC which is endorsed.

Laboratory related TEAEs including ALT and AST increased and total bilirubin were comparable between treatment groups. No laboratory-related TEAEs were considered serious. Treatment emergent AEs that led to discontinuation of test article occurred in 2 omadacycline subjects (Subjects 1200-332-5002 and 1200-376-5046) and 2 moxifloxacin subjects (Subjects 1200-311-5010 and 1200-420-5004) who discontinued due to TEAEs of ALT and/or AST increased.

Table S24. Liver Chemistry Elevations for Subjects with Normal Baseline Values (AC3 Pool)

Lab Parameter (SI unit)	Parameter	Omadacycline N = 1073 n (%)	Linezolid N = 689 n (%)	Moxifloxacin N = 388 n (%)
ALT (U/L)				
Normal at Baseline, N1		772	537	295
Meeting criterion at post-Baseline	> 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, N1		858	561	328
Meeting criterion at post-Baseline	> 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
ALT or AST (U/L)				
Normal at Baseline, N1		718	494	271
Meeting criterion at post-Baseline	> 3 × ULN	15 (2.1)	19 (3.8)	12 (4.4)
	> 5 × ULN	9 (1.3)	6 (1.2)	1 (0.4)
	> 10 × ULN	5 (0.7)	3 (0.6)	0
Total bilirubin (µmol/L)				
Normal at Baseline, N1		937	593	364
Meeting criterion at post-Baseline	> 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, N1		819	523	311
Meeting criterion at post-Baseline	> 2 × ULN	5 (0.6)	1 (0.2)	6 (1.9)
ALT or AST and total bilirubin assessed at same visit post-Baseline				
Normal at Baseline, N1		639	434	254
Meeting criterion at post-Baseline	ALT or AST > 3 × ULN, total bilirubin > 2 × ULN	2 (0.3)	0	0
	ALT or AST > 5 × ULN, total bilirubin > 2 × ULN	2 (0.3)	0	0
	ALT or AST > 10 × ULN, total bilirubin > 2 × ULN	2 (0.3)	0	0
ALT or AST and total bilirubin assessed at any time post-Baseline				
Normal at Baseline, N1		639	434	254
Meeting criterion at post-Baseline	ALT or AST > 3 × ULN, total bilirubin > 2 × ULN	2 (0.3)	0	0
	ALT or AST > 5 × ULN, total bilirubin > 2 × ULN	2 (0.3)	0	0
	ALT or AST > 10 × ULN, total bilirubin > 2 × ULN	2 (0.3)	0	0
ALP and total bilirubin assessed at same visit post-Baseline				
Normal at Baseline, N1		739	484	300
Meeting criterion at post-Baseline	ALP > 2 × ULN, total bilirubin > 2 × ULN	1 (0.1)	0	1 (0.3)

Source: ISS Table 14.3.3.8.4.2.

Vital signs

No significant impact of omadacycline on SBP, DBP and ECG parameters PR, RR, QRS and QT values was noted with omadacycline in the phase 2/3 program. 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, although the decline over time was less rapid for omadacycline subjects compared to moxifloxacin subjects.

Cardiac Safety report (phase 1 study)

PTK 0796-TQTC-0803 was a randomised, placebo-controlled, double blind, double-dummy TQTc cross-over study conducted in 64 healthy subjects who received single iv doses of PTK 0796 100 mg, 300 mg, placebo, and 400 mg moxifloxacin po in separate treatment periods.

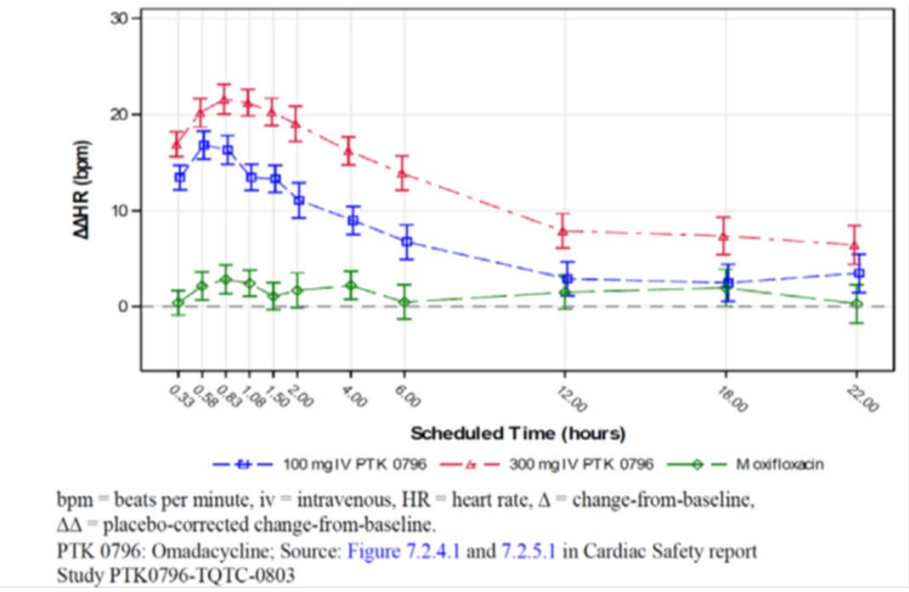
Effect on Heart Rate

A single iv dose of 100 mg and 300 mg PTK 0796 resulted in a clear effect on heart rate with the largest mean placebo-corrected ΔHR observed at early time-points (16.8 bpm at 35 minutes post-dose after the 100 mg dose and 21.6 bpm at 50 minutes after dosing with 300 mg). Mean ΔΔHR thereafter declined but remained above 5 bpm during 6 hours after the omadacycline 100 mg dose and for the full observation period up to 22 hours after the 300 mg dose.

Omadacycline did not have an effect on cardiac conduction as shown for PR, QRS and ATcS intervals.

The thorough cardiac safety and QTc study TR701 115 evaluated omadacycline for its potential to induce QT interval prolongations in healthy subjects and indicated no concern.

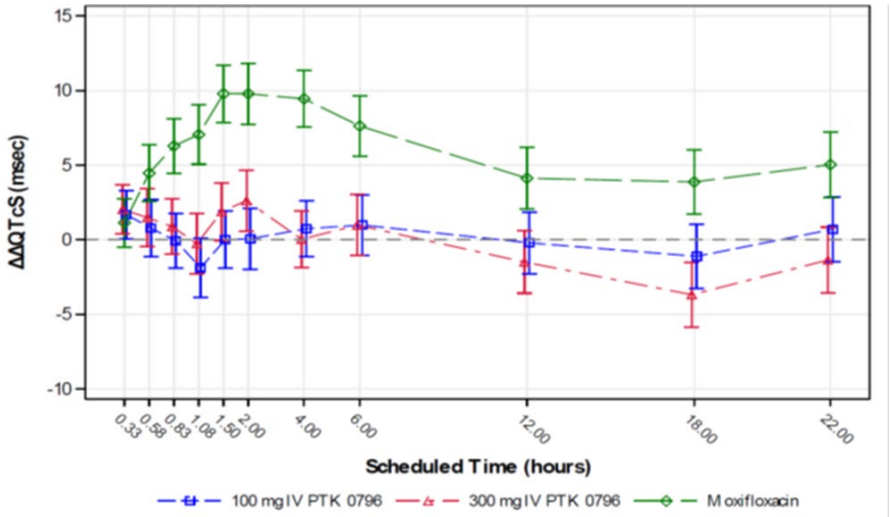
Figure 8. Placebo-Corrected ΔHR Across Post-Dosing Timepoints, PTK0796-TQTC-0803



bpm = beats per minute, iv = intravenous, HR = heart rate, Δ = change-from-baseline, ΔΔ = placebo-corrected change-from-baseline.
PTK 0796: Omadacycline; Source: Figure 7.2.4.1 and 7.2.5.1 in Cardiac Safety report Study PTK0796-TQTC-0803

Source: Figure 7.2.4.1 and 7.2.5.1 Cardiac Safety report

Figure 9. Panel B: Placebo-Corrected ΔQTcS (ΔΔQTcS) Across Post-Dosing Timepoints in PTK0796-TQTC-0803



Δ = change-from-baseline, ΔΔ = placebo-corrected change-from-baseline, HR = heart rate, msec = milliseconds, QTcS = individualized HR-corrected QT interval.
PTK 0796: Omadacycline; Source: Figure 7.2.4.6 and 7.2.5.6 in Cardiac Safety report Study PTK0796-TQTC-0803

Figure 7.2.4.6 and 7.2.5.6 Cardiac Safety report

Safety in special populations

Age

All age groups, < 65 years, > 65 to 75 years and > 75 years of age had a similar frequency of TEAEs in the omadacycline arm (48%, 49.6% and 48%, respectively) with gastrointestinal side effects as the most abundant events. The age group < 65 years of age showed the highest rate of nausea and vomiting. The Applicant has provided a more detailed table for the different type and severity stages of AEs for the age groups < 65 years, 65-74 years, 75-84 years and >= 85 years which did not reveal any safety concerns

Diabetes

Omadacycline subjects who reported at least 1 TEAE was comparable in subjects with a history of diabetes compared to subjects without a history of diabetes. The most notable event between omadacycline subjects with and without a history of diabetes (based on a ≥ 5% difference) was nausea, which occurred in a higher percentage of omadacycline subjects without a history of diabetes. In addition, TEAEs of diarrhoea were reported by a higher percentage of subjects with a history of diabetes (10.5%) than those without diabetes (2.8%) in the omadacycline group in the A3 Pool. No differences in diarrhoea were observed in the C3 Pool.

COPD/asthma

The percentage of subjects who had at least 1 TEAE was higher in subjects with a history of asthma/COPD (56.5% omadacycline, 55.3% moxifloxacin) compared to subjects without a history of asthma/COPD (36.7% omadacycline, 46.8% moxifloxacin). The few notable events (based on a ≥ 5% difference) were as follows:

- Constipation events occurred in a higher percentage of subjects with a history of asthma/COPD (8.2% omadacycline, 3.9% moxifloxacin) compared to subjects without a history of asthma/COPD (0.7% omadacycline, 1.0% moxifloxacin).

- Nausea events occurred in a higher percentage of subjects with a history of asthma/COPD (7.1% omadacycline, 6.6% moxifloxacin) than subjects without a history of asthma/COPD (1.0% omadacycline, 5.1% moxifloxacin).
- Vomiting events occurred in a higher percentage of omadacycline subjects with a history of asthma/COPD (7.1% omadacycline, 1.3% moxifloxacin). Subjects without a history of asthma/COPD had similar rates of vomiting in the omadacycline and moxifloxacin groups.

Hepatic impairment

Study CPTK796A-2201 investigated subjects with varying degrees of hepatic impairment (mild, moderate and severe). The primarily affected SOCs were nervous system disorder, gastrointestinal disorders, general disorders and administration site conditions. Headache (13.3%), nausea (6.7%), infusion site pain (6.7%), contusion (6.7%) and dizziness (6.7%) were the most commonly experienced AEs. No death occurred in this study. One subject experienced SAEs of severe intensity related to alcohol poisoning (intoxication), angina pectoris, hypocalcaemia, hypotension and rhabdomyolysis. None of the events were suspected to be related to the study medication. Another subject was discontinued from the study due to an AE of mild rash, which was considered possibly related to the study medication. In addition, no clinically relevant changes in clinical laboratory tests or physical examination findings including heart rate were reported.

Renal impairment

Study PTK0796-RENL-15102 investigated subjects with end-stage renal disease (ESRD) on hemodialysis compared to healthy adults. Overall, 5 of 16 subjects experienced a total of 8 TEAEs during the study. The TEAEs included upper respiratory infection (2), viral upper respiratory infection, dizziness, headache, infusion site erythema, bronchospasm, and rash papular. One additional subject had an AE of injection site hematoma that was not treatment-emergent. Only the dizziness and rash were considered related to the study drug. There were no SAEs or deaths reported. No subjects withdrew from the study due to an AE, and there were no AEs resulting in study drug discontinuation or interruption. Although individual changes from baseline were observed in chemistry, haematology, and urinalysis values, no apparent clinically relevant trends were observed.

Paediatric use

There have been no studies of omadacycline in children. All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature human infants given po tetracycline. This reaction was shown to be reversible when the drug was discontinued. Accordingly, children less than 8 years of age should not receive omadacycline.

Use in pregnancy and lactation

Omadacycline may cause fetal harm when administered to a pregnant woman. Reproductive toxicity studies suggest that omadacycline may affect the developing fetus during the organogenesis period, resulting in abortion or reduced fetal body weight. Pregnant women should not receive omadacycline.

It is not known whether omadacycline is excreted in human milk. During tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) omadacycline, like all tetracyclines, may cause permanent discoloration of the teeth. Until more is known, nursing women should not receive omadacycline.

Safety related to drug-drug interactions and other interactions

No safety relevant aspects have been detected in studies investigating the potential for drug-drug interactions of omadacycline.

Discontinuation due to AES

Discontinuation rates due to TEAES were overall low and comparable between omadacycline and the comparator arms. A systematic occurrence of a specific type of TEAE leading to discontinuation of treatment is not observed in the different treatment arms.

Immunological events - N/A

Post marketing experience – N/A

3.3.11. Discussion on clinical safety

Overall, 1947 subjects received at least 1 dose of omadacycline. Of these 1252 subjects have been exposed to omadacycline in the frame of the phase 2/3 study programme obtaining 100 mg iv / 300mg orally of the test drug once daily for eight to nine days in average which roughly corresponds to the recommended dosage (100 mg iv/300mg oral once daily for 7 to 14 days).

The most common adverse events associated with omadacycline in phase 2 and 3 studies were nausea (15.3%), vomiting (8.0%), headache (4.2%), ALT increased (3.7%), AST increased (3.0%), diarrhoea (2.6%), cellulitis (2.4%), wound infection (2.4%), constipation (2.2%) and infusion site extravasation (2.2%). The Applicant has provided an adequate rationale for terms included in the SmPC as outlined in the answer to question 230. The SmPC will be adjusted according to the strategy presented.

The most frequent type of AEs across all pools was gastrointestinal events, with higher frequencies under omadacycline compared to linezolid or moxifloxacin. The highest rates of nausea and vomiting events were reported in the Phase 3 ABSSSI oral-only study, the majority of these TEAEs occurred during the "loading dose" phase on Days 1 and 2 of the treatment. These TEAEs were also more common during the po than iv administration in studies, which used both ways of application. Concomitant anti-emetic therapy was used in almost half of the subjects experiencing GIT AEs. Gastrointestinal events are known and generally manageable tetracycline class effects. Based on the food interaction PK studies revealing decreased exposure to omadacycline when administered following a meal the Applicant proposed the administration of this medicinal product under fasting condition which is agreed. The proposed precaution and listed AEs related to the gastrointestinal disorders in SmPC are considered sufficient at this time. The effect of a light meal on tolerability is being evaluated in an ongoing study. Further information on the outcome of the study will be provided, when the study is completed and reported.

Across the omadacycline clinical development programme, there were 10 (0.8%) omadacycline and 7 (0.6%) comparator subjects who died. An imbalance in the mortality rate is noted in the CABP study between omadacycline (2.1%) and moxifloxacin (1.0%), (95% CI -0.7 to 2.8). Narrative evaluation by the Rapporteur revealed that five of the fatal cases, comprising vascular (1), cardiac (3) and cerebrovascular (1) events, may be a result of the underlying cardiovascular and pulmonary comorbidities presented by the patients. In one case, the patient was re-admitted for a new (likely hospital-acquired) pneumonia episode caused by non-susceptible organisms. In two cases, patients experienced a severe rapid deteriorating CABP disease, secondary in at least one case to known non-susceptible organisms. Overall, the relatedness of the imbalance to the treatments received is unclear. Only a larger study population would permit more reliable evaluation of any true difference.

It is noted that FDA has included a short statement regarding the outcome of mortality rates in the CABP-1200 study in the US prescribing information in section Warnings/Precautions, and furthermore included as a post marketing requirement that a trial similar to the CABP-1200 study design, should be performed to further evaluate the safety signal of the mortality imbalance in the CABP trial (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209816_209817lbl.pdf). The Applicant has specified the planned additional study to be performed in compliance with study design suggestions made by the FDA. The Applicant intends to perform an additional study with the primary endpoint of efficacy (early clinical response) including 450 to 670 POST Risk Class III and IV subjects. A Data Monitoring Committee will review safety data, including deaths throughout the trial. The study will be completed November 2022 (reporting April 2023 to EMA and FDA).

Allergic reactions were not frequently observed with omadacycline and included the PTs pruritus, rash, urticaria and hypersensitivity reactions. Pruritus and rash have been included in the SmPC as uncommon events under "skin reactions". Erythema has been included as an uncommon event in the SmPC. Furthermore, hypersensitivity reaction has been included in the SmPC as uncommon event which is endorsed.

In principal, no clinically meaningful changes of haematology parameters and electrolytes from the baseline were observed which were related in a negative way to omadacycline treatment. Of note, in several cases lower neutrophil counts were observed with omadacycline (>1% with a >= 2 Grade decrease). The investigation of cases narratives (5) did not reveal a causative association with drug treatment. Thrombocytes did not decrease significantly in omadacycline treated subjects. Based on further analyses demonstrating that 1% of individuals show at least one episode of moderate thrombocytosis post-baseline and a clear treatment-event relationship in several individuals experiencing a TEAE of thrombocytosis, it is suggested to include thrombocytosis as often occurring event in the SmPC.

No subject had a TEAE of acute pancreatitis under treatment with omadacycline. Of note, grade 2 increase of amylase and lipase values was observed in 22 (2,1%) and 61 (5,9%) omadacycline subjects with isolated cases of > 10 time increase of amylase. Out of 22 cases, only 3 subjects showed amylase values over 3 xULN. One of them showed in parallel increased lipase levels without nausea, vomiting or abdominal pain. TEAEs of nausea, vomiting or abdominal pain were neither reported for the remaining 2 cases. 11 omadacycline subjects (out of 61 with the grade 2 lipase increase) showed nausea, vomiting or abdominal pain without more serious clinical patterns potentially indicating symptoms of acute pancreatitis. Out of 5 TEAEs of increased amylase or lipase, only one subject experienced increase in both values (amylase 1,2xULN, lipase 2,2xULN) without concomitant symptoms. No safety issue was identified based on the provided data.

No clinically significant impact of omadacycline on ECG parameters (PR, RR, QRS, QT) is noted in the phase 2/3 pool with the exception of an increased heart rate. 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 over treatment time for omadacycline subjects compared to moxifloxacin subjects. Post-baseline elevations of HR were seen in 1.4% of omadacycline treated subjects and were slightly less common compared to comparators. It is suggested to include tachycardia as common event in the SmPC.

The overall incidence of TEAEs showed no major differences with respect to subpopulations, i.e., age, sex, race, and BMI, and underlying disease characteristics relating to renal function, hepatic function, and diabetes, was analysed. No major shifts in the AE profile have been identified in relation to these parameters.

3.3.12. **Conclusions on clinical safety**

The safety profile of omadacycline appears generally acceptable. An imbalance in the mortality rate is noted in the CABP study between omadacycline (2.1%) and moxifloxacin (1.0%), for which the reason is not known. This poses an uncertainty with regard to unfavourable effects of the test drug.

3.4. Risk management plan

3.4.1. **Safety Specification**

Summary of safety concerns

The following changes to the list of safety concerns have been implemented in the RMP Version 0.3:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

3.4.2. **Discussion on safety specification**

The implemented changes to the safety concerns are endorsed, based on the argumentation summarized below.

3.4.3. **Conclusions on the safety specification**

In the first round it was proposed including ***"Dental enamel hypoplasia, teeth discoloration and reversible bone growth depression in infants exposed in utero or through maternal milk"*** *as an important potential risk:* Omadacycline may cause foetal harm when administered to a pregnant woman. Reproductive toxicity studies in animals suggest that omadacycline may affect the developing foetus during the organogenesis period, resulting in abortion or reduced foetal body weight. It is not known whether omadacycline is excreted in human milk. During tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) omadacycline, like all tetracyclines, may cause permanent discoloration of the teeth. The applicant suggests routine pharmacovigilance activities for a follow up of these events (PSURs) which is endorsed. A special warning is included in the SmPC to avoid using the drug during pregnancy and in young individuals. No additional PV activities will take place. Therefore, the item was removed from the list of safety concerns.

'***Immunosuppressed individuals, resulting in a loss in efficacy***': Following EMA recommendations, it is expected that the Applicant will monitor this aspect as an efficacy issue in the PSURs. The item has been removed from the list of safety concerns, which is endorsed.

'***Prolonged treatment for more than 14 days***': The absence of data itself does not automatically constitute a safety concern. The Applicant has removed this item from the list of safety concerns and will monitor this aspect through PSURs, which is endorsed.

Regarding **"*Bacterial resistance*"** see comments in 3.4.4.

3.4.4. **Pharmacovigilance plan**

Summary of planned additional PhV activities from RMP

There are no ongoing or planned omadacycline category 1 to 3 studies.

The Applicant proposed **bacterial resistance** as important potential risk during the first round. Following EMA recommendations, it is expected that the applicant will monitor this as an efficacy issue in the PSURs. The applicant has consecutively deleted this item from the list of safety concerns, which is endorsed.

During the third round the Applicant has updated the list of safety concerns (no issues listed) and the section regarding activities in the frame of the pharmacovigilance plan, accordingly.

The safety concerns to be discussed in the PSURs include:

- Bacterial resistance
- Treatment in immunosuppressed individuals, resulting in a loss in efficacy
- Prolonged treatment for more than 14 days
- Safety in pregnancy and lactation
- Phototoxicity
- Dental enamel hypoplasia, teeth discoloration and reversible bone growth depression in infants exposed in utero or through maternal milk

3.4.5. **Risk minimisation measures**

The paragraph describing risk minimisation contains the following information in the RMP Version 0.3:

V.1. Routine Risk Minimisation Measures

Routine risk minimization measures are risk communications through product information, labeling, or packaging. The risks associated with the use of omadacycline are discussed under the appropriate sections of the SmPC.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation measures as described in Part V.1 are considered sufficient for omadacycline. Therefore, no additional risk minimisation measures are proposed.

V.3. Summary of Risk Minimisation Measures

Routine risk minimization measures and routine pharmacovigilance activities are considered sufficient for omadacycline.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4.6. **Conclusion on the RMP**

The CHMP and PRAC considered that the risk management plan version 0.3, dated 31-07-19, is acceptable.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the European Birth Date (EBD) or international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

The applicant should indicate if they wish to align the PSUR cycle with the EBD or the IBD.

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. **Disease or condition**

The indications applied for are treatment of adults with:

- Acute bacterial skin and skin structure infections (ABSSSI)
- Community-acquired pneumonia (CAP)

Acute bacterial skin and skin structure infections (ABSSSI) are generally caused by Gram positive pathogens including *S. aureus* and *Streptococcus* spp.. They can be serious, limb- or life-threatening conditions, often requiring systemic antibiotic therapy and possibly surgical management and hospitalisation.

Community-acquired pneumonia is caused most frequently by *S. pneumoniae, Haemophilus influenzae*, and some atypical pathogens such as *Mycoplasma pneumoniae* and *Legionella pneumophila*, but can also involve rarer atypicals and Gram negative organisms. CABP is classified separately from Hospital-acquired pneumonia (HAP) (developing ≥48 hours after hospital admission), Ventilator-acquired pneumonia (VAP) or Health-care associated pneumonia (HCAP), which are caused by a different range of pathogens. Management includes systemic antibiotic therapy and supportive care.

4.1.2. **Available therapies and unmet medical need**

The most commonly used classes of antibiotics for ABSSSI and CAP include beta-lactams, lipopeptides, oxazolidinones, glycopeptides and tetracyclines, and for CAP additionally macrolides, fluoroquinolones are sometimes used, for coverage of atypical pathogens. Omadacycline does not address an unmet need, but would provide a further antibiotic option.

4.1.3. **Main clinical studies**

The clinical programme for omadacycline comprises two pivotal Phase 3 clinical studies in ABSSSI and one single pivotal Phase 3 study in CAP.

Studies PTK0796-ABSI-1108 (n=655) and PTK0796-ABSI-16301 (n=735) were similarly designed, 1:1 randomised, active-controlled, double-blinded Phase 3 non-inferiority studies of 7-14 days' iv-to-po or po-only (respectively) treatment with omadacycline, against authorised comparator Linezolid, in treatment of adults with ABSSSI (comprising cellulitis/erysipelas, major abscess, wound infection) known or suspected to be caused by Gram positive pathogens, associated with signs of a systemic inflammatory response.

Study PTK0796-CABP-1200 (n=660) was a 1:1 randomised, double-blind, active-comparator-controlled, multi-centre Phase 3 non-inferiority study comparing 7-14 days' treatment with an iv-to-po regimen of omadacycline, against an iv-to-po regimen of authorised comparator moxifloxacin, for the treatment of adults with CABP, in PORT Risk Class III or IV and not requiring intensive care.

4.2. Favourable effects

ABSSSI

Study PTK0796-ABSI-1108 demonstrated high rates of overall clinical response at PTE (the EU primary efficacy endpoint) in both treatment arms in both the mITT population (86.1% omadacycline, 83.6% linezolid) and CE-PTE population (96.3% omadacycline, 93.5% linezolid). The difference between treatment arms was 2.5 (95% CI -3.2, 8.1) in the mITT population and 2.8 (95% CI -0.9, 7.1) in the CE-PTE population.

Study PTK0796-ABSI-16301 also demonstrated high rates of overall clinical response at PTE (the EU primary efficacy endpoint) in both treatment arms in both the mITT population (84.2% omadacycline, 80.8% linezolid) and CE-PTE population (97.9% omadacycline, 95.5% linezolid). The difference between treatment arms was 3.3 (95% CI -2.2, 9.0) in the mITT population and 2.3 (95% CI -0.5, 5.8) in the CE-PTE population.

Given that the lower limit of the 95% CI for the treatment difference between arms in the mITT and CE populations was above the pre-specified margin of -10%, omadacycline was demonstrated non-inferior to linezolid in both studies, according to the EMA statistical analysis plan.

CAP

The single pivotal trial PTK0796-CABP-1200 demonstrated high rates of overall clinical response at PTE (the EU primary efficacy endpoint) in both treatment arms in both the ITT population (84.2% omadacycline, 80.8% moxifloxacin) and CE-PTE population (97.9% omadacycline, 95.5% moxifloxacin). The difference between treatment arms was 3.3 (97.5% CI -2.2, 9.0) in the ITT population and 2.3 (97.5% CI -0.5, 5.8) in the CE-PTE population. Given that the lower limit of the 97.5% CI for the treatment difference between arms in the ITT and CE populations was above the pre-specified margin of -10%, iv/po omadacycline was demonstrated non-inferior to iv/po moxifloxacin, according to the EMA statistical analysis plan, using a 1-sided alpha level of 0.0125.

Sub-group analysis revealed, perhaps unsurprisingly, numerically higher rates of clinical success amongst subjects with PORT Risk Class III vs IV (90.7% vs 83.3% for omadacycline, 88% vs 80% for moxifloxacin).

4.3. Uncertainties and limitations about favourable effects

In the absence of a traditional dose finding study, PK/PD and PTA data provide important alternative support for the dose selected for Phase 3 studies. Several deficiencies in the non-clinical PK/PD package and PTA analysis mean that support in this application for dose selection is not robust. Success rates were high in the clinical studies even for pathogens with MIC values several dilutions above the highest MIC expected to be covered according to PTA analysis, and clinical success rates did not appear to correlate to species or MIC. The lack of comprehensive PK-PD support for efficacy of the proposed dose is mitigated for the ABSSSI infection by a sufficient quantity of clinical outcome data. However, this is not true for CAP, where there is a clear lack of support for all proposed dosing regimens to cover key pathogens, and only a single clinical study has been conducted. The Applicant considers that nonclinical PK-PD PTA data may not be as predictive for certain classes of antibiotics (tetracyclines for instance). If this is so, this makes it more difficult to justify an indication based on a single pivotal trial; non-predictivity of PK/PD does not in any way strengthen the evidence that can be derived from a single pivotal trial.

Clinical success rates were very similar between the two ABSSSI studies, i.e. regardless of iv-to-po or po dosing regimen and are generally consistent with those seen in previous studies. For example, the rates of clinical success based on IACR at PTE were 88% in the ITT population and 96% in the CE population for linezolid, in a recent iv to po clinical trial in ABSSSI subjects (Moran, *et al.*, 2014). Sensitivity analyses, including analysis of the co-primary endpoint in the all-treated population and analysis assuming subjects with indeterminate clinical outcomes to be clinical success, were supportive of the primary analysis.

Clinical success rates in the treatment of CABP were numerically lower for omadacycline compared to moxifloxacin in eradication of some gram-negative bacteria, namely *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Klebsiella pneumoniae*. This aligns with the observed less potent *in vitro* activity of omadacycline against Gram negative species.

4.4. Unfavourable effects

The most common events in omadacycline subjects included side effects at the gastrointestinal tract of mild to moderate intensity (see effects table).

An imbalance in the mortality rate is noted in the CABP study between omadacycline and moxifloxacin (2.1% for omadacycline (8 cases) versus 1.0% for moxifloxacin (4 cases)), with a rate difference of 1.1% (95%CI -0.7 to 2.8). Based on a request from the FDA, the Applicant plans to perform an additional post-marketing study of CABP to further investigate the observed imbalance.

While no impact of omadacycline on heart conduction was observed, the heart rate was significantly increased after a single iv omadacycline dose (100 mg, 300 mg) in the TQTc study. The peak is approximately within the first 60 minutes after administration and the increases in heart rate are dose related. The thorough cardiac safety and QTc study evaluated omadacycline for the potential for QT interval prolongation in healthy subjects indicated no concern. No clinically significant impact of omadacycline was noted on SBP and DBP and ECG parameters (PR, RR, QRS, QT) in the phase 2/3 pool. Analyses of the mean change over time in HR showed a slower decline in the omadacycline arm over treatment time compared to comparator arms. Comparable elevations in HR (> 120bpm or elevation by > 15bpm from baseline) post baseline where observed in 1.4% omadacycline and 2.2% linezolid treated subjects respectively.

4.5. Uncertainties and limitations about unfavourable effects

A numerical difference of eight (2.1%, omadacycline) and four cases of death (1,0%, moxifloxacin arm) have been observed in the CABP study, the reason for which is unknown.

4.6. Effects Table

Effects Table for Omadacycline

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ABSSSI						
Overall clinical response at PTE visit	Based on IACR at TOC and PTE visits	%	**Omadacycline** mITT 86.1 Difference=2.5	**Linezolid** mITT 83.6	(95% CI -3.2, 8.1) Non-inferior	PTK0796-ABSI-1108
			CE-PTE 96.3 Difference=2.8	CE-PTE 93.5	(95% CI -0.9, 7.1) Non-inferior	
			Omadacycline mITT 84.2 Difference=3.3	**Linezolid** mITT 80.8	(95% -2.2, 9.0) Non-inferior	PTK0796-ABSI-16301
			CE-PTE 97.9 2.3	CE-PTE 95.5	(95% -0.5, 5.8) Non-inferior	
CABP						
Overall clinical response at PTE visit	Based on IACR at TOC and PTE visits	%	**Omadacycline** mITT 88.4 Difference=3.3	**Moxifloxacin** mITT 85.2	Single pivotal study, no PKPD support (97.5% CI -2.7, 9.3) Non-inferior	PTK0796-CABP-1200
			CE-PTE 92.5 Difference=2.0	CE-PTE 90.5	(97.5% CI -3.2, 7.4) Non-inferior	
Unfavourable Effects						
Nausea	Based on the SC23 pool	%	Omadacycline 15.3	Linezolid/Moxifl. 10.0/5.4	Strong evidence	SC23 pool
Vomiting	Based on the SC23 pool	%	Omadacycline 8.0	Linezolid/Moxifl. 4.8/1.5	Strong evidence	SC23 pool
Diarrhoea	Based on the SC23 pool	%	Omadacycline 2.6	Linezolid/Moxifl. 4.6/8.0	Strong evidence	SC23 pool
Deaths	Within the CABP study	%	omadacycline 2.1	Moxifloxacin 1.0	Non-negligible numeric difference No clear trend towards therapy failure or specific side effects	PTK0796-CABP-1200

Abbreviations: SC23 pool (comprises all 5 phase 2/3 studies), CABP study (includes patients with pneumonia)

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

The clinical success rates for treatment of both ABSSSI and CABP were high across the pivotal Phase 3 studies and aligned with those reported in recent studies of authorised comparators. Omadacycline demonstrated non-inferiority to authorised comparators used in these indications and the statistical

results were robust and supported by sensitivity analyses. Clinical outcome did not appear correlated to MIC, and organisms with omadacycline MIC values up to 16 µg/mL were successfully treated according to overall clinical response at PTE.

The tolerability of omadacycline is good.

A numeric imbalance of mortality has been observed in the CABP study. It is possible that this is a chance finding, but this non-negligible difference does create a further caveat with regard to the appropriateness of approving omadacycline for CABP based on a single pivotal study.

4.7.2. **Balance of benefits and risks**

ABSSSI

Omadacycline is considered to have demonstrated good safety and tolerability and high clinical success rates, comparable to an authorised comparator and recently published studies, in two Phase 3 studies of ABSSSI, and this suggests that omadacycline could offer an alternative to current antibiotic options, with generally acceptable safety and tolerability. An advantage in comparison to several already authorised tetracyclines is preserved activity in the presence of many common tetracycline-specific resistance mechanisms. Omadacycline is available in both iv and po formulations, albeit with fasting requirements when administered po.

Considering all findings, the favourable effects of omadacycline are considered to outweigh the unfavourable effects for the treatment of ABSSSI.

CAP

Evidence for clinical efficacy in CAP comes from a single pivotal study, in which a non-negligible numeric imbalance in mortality was observed. A causative association could not be identified from careful examination of the individual cases but cannot be ruled out. The applicant plans to perform an additional post-marketing study in CAP at the request of FDA.

At present, study PTK0796-CABP-1200 has not fulfilled the requirements of a single pivotal study, the objective of which is to confirm an already established hypothesis. Additional efficacy and safety data from the planned further study in CAP will be required before a decision can be made on the B/R balance for omadacycline in CAP, for the purposes of authorisation for this indication (**MO B/R**).

4.8. Conclusions

The overall B/R of omadacycline is negative.

5. QRD checklist for the review of user testing results

PRODUCT INFORMATION

Name of the medicinal product:	Nuzyra
Name and address of the applicant:	Paratek Ireland Limited, Dublin, Ireland
Name of company which has performed the user testing:	NDA Regulatory Science Ltd, UK
Type of Marketing Authorisation Application:	New application
Active substance:	Omadacycline tosylate
Pharmaco-therapeutic group (ATC Code):	**J01AA**
Therapeutic indication(s):	for the treatment of adults with the following infections (see sections 4.4 and 5.1): - Community-acquired bacterial pneumonia (CABP) - Acute bacterial skin and skin structure infections (ABSSSI)
Orphan designation	☐ **yes** ☒ **no**
Rapporteur/CoRapporteur	SE/CZ

- Full user testing report provided	☒ yes	☐no
- Focus test report provided	☐ yes	☒no
- Bridging form provided[1]	☒ yes	☐no

- In case bridging form[1] has been provided, please perform the assessment in the bridging form and state the overall conclusion/recommendations below:

A bridging report covering the IV formulation has been provided, referring to the full test for the oral formulation. The bridging is acceptable.

- Is the justification for bridging acceptable?	☒ yes	☐ no

[1] QRD form for submission and assessment of user testing bridging proposals [EMA/355722/2014]

1. Technical assessment

1.1 Recruitment

- Is the interviewed population acceptable? ☒ yes ☐ no ☐ no information

Comments/further details:

1.2 Questionnaire

- Is the number of questions _____ sufficient? ☒ yes ☐ no ☐ no information
- Questions cover significant (safety) issues for the PL concerned? ☒ yes ☐ no ☐no information

Comments/further details:

1.3 Time aspects

- Is the time given to answer acceptable? ☒ yes ☐ no ☐ no information
- Is the length of interview acceptable? ☒ yes ☐ no ☐ no information

Comments/further details:

1.4 Procedural aspects

- Rounds of testing including pilot _____ ☐ yes ☐ no ☐ no information

Comments/further details:

1.5 Interview aspects

- Was the interview conducted in well structured/organised manner? ☒ yes ☐ no ☐ no information

Comments/further details:

2. Evaluation of responses

2.1 Evaluation system

- Is the qualitative evaluation of responses acceptable? ☒ yes ☐ no ☐ no information

- Does the evaluation methodology satisfy the minimum prerequisites? ☒ yes ☐ no ☐ no information

Comments/further details:

2.2 Question rating system

- Is the quantitative evaluation of responses acceptable? ☒ yes ☐ no ☐ no information

Comments/further details:

3. Data processing

- Are data well recorded and documented? ☒ yes ☐ no ☐ no information

Comments/further details:

4. Quality aspects

4.1 Evaluation of diagnostic questions

- Does the methodology follow Readability guideline Annex? ☒ yes ☐ no ☐ no information

- Overall, each and every question meets criterion of 81% correct answers (e.g. 16 out of 20 participants) ☒ yes ☐ no ☐ no information

Comments/further details:

4.2 Evaluation of layout and design

- Follows general design principles of Readability guideline ☒ yes ☐ no
- Language includes patient friendly descriptions ☒ yes ☐ no
- Layout navigable ☒ yes ☐ no
- Use of diagrams acceptable ☐ yes ☐ no

Comments/further details:

5. Diagnostic quality/evaluation

- Have any weaknesses of the PL been identified? ☒ yes ☐ no
- Have these weaknesses been addressed in the appropriate way? ☒ yes ☐ no

Comments/further details:

Both language and layout have been adjusted according to the result of the user consultation.

6. Conclusions

- Have the main objectives of the user testing been achieved? ☒ yes ☐ no
- Is the conclusion of applicant accurate? ☒yes ☐ no
- Overall impression of methodology ☒ positive ☐ negative
- Overall impressions of leaflet structure ☒ positive ☐ negative

CONCLUSION/OVERVIEW

The user consultation is found acceptable for both the content and layout.