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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Zerbaxa

International non-proprietary name: ceftolozane / tazobactam

Procedure No. EMEA/H/C/003772/0000

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List of abbreviations

AE	Adverse event
AI	Accumulation index
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Active systemic anaphylaxis
AST	Aspartate aminotransferase
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CDAD	Clostridium difficile associated diarrhea
cIAI	Complicated intra-abdominal infections
CL	Clearance
Cmax	Maximum concentration
CPK	Creatine phosphokinase
CPPs	critical quality attributes
CQAs	Critical Process Parameters
CrCL	Creatinine clearance
CRP	C-reactive protein
CSR	Clinical study report
cUTI	Complicated urinary tract infections
CXA	Ceftolozane
CYP	Cytochrome P450
DDI	Drug-drug interaction
DPI	Drug Product Intermediate
DEREK	Deductive Estimation of Risk from Existing Knowledge
DSMB	Data Safety Monitoring Board
ECF	Extracellular fluid (volume)
ECG	Electrocardiogram
ESBL	Enterobacteriaceae
eDISH	Evaluation of drug-induced serious hepatotoxicity
EMA	European Medicines Agency
EOT	End of treatment
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
GC	Gas chromatography
GLP	Good laboratory practice
GTIs	Genotoxic impurities
hERG	Human ether-à go-go related gene
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
IAI	Intraabdominal infection
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International normalization ratio
IR	Infrared spectroscopy
ISS	Integrated Summary of Safety
IV	Intravenous
KF	Karl Fischer
Ki	Inhibitor constant
kg	Kilogram
L	Liter

LFT	Liver function test
LLN	Lower limit of normal
LFU	Late follow up
MATE	Multidrug and toxic extrusion
Max	Maximum
MCV	Mean corpuscular volume
MD	Multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration that inhibits x% of the microbial strains
min	Minimum
mL	Milliliter
mmHg	Milliliters of mercury
MRSA	Methicillin-resistant Staphylococcus aureus
MS	Mass Spectrometry
ms	Milliseconds
n	Number of patients
NA	Not applicable
NMR	Nuclear Magnetic Resonance
NOAEL	No observed adverse effect levels
OAT	Human organic anion transporter
PBT	Persistent, bioaccumulative and toxic
PCS	Potentially clinically significant
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
PND	Postnatal day
PT	Prothrombin time
QTPP	Quality Target Product Profile
RH	Relative humidity
SMs	starting materials
UV	Ultra violet spectroscopy
PPB	Plasma Protein Binding
Q_1 , Q_3	Quartile range
QTc	Corrected QT
QTcB	Corrected QT according to Bazett
QTcF	Corrected QT according to Fridericia
ROW	Rest of world
SAE	Serious adverse event
SAP	Statistical analysis plan
SCS	Summary of Clinical Safety
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SOC	System organ class
t1/2	Elimination half-life
TK	Toxicokinetic
tQT	Thorough QT
ULN	Upper limit of normal
UTI	Urinary tract infection
Vd	Volume of distribution
WBC	White blood cells

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Cubist (UK) Limited submitted on 29 July 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zerbaxa, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2013.

The applicant applied for the following indication:

"Zerbaxa is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):
- Complicated intra-abdominal infections in combination with metronidazole
- Complicated urinary tract infections, including pyelonephritis

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

The applicant has changed from Cubist (UK) Limited to Merck Sharp & Dohme Limited at the time of the responses to the day 180 LoOI.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ceftolozane (sulfate) was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0126/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0126/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance ceftolozane (sulfate) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21/02/2013. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings

Co-Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 29 July 2014.
- The procedure started on 20 August 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2014 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 November 2014 (Annex 2).
- PRAC RMP Advice and assessment overview, adopted by PRAC on 4 December 2014 (Annex 3).
- During the meeting on 18 December 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 December 2014 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 March 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 April 2015 (Annex 5).
- During the CHMP meeting on 21 May 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 6).
- The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product:
  - A GCP inspection has been conducted for the trials CXA-cUTI-10-04 and CXA-cUTI-10-05 at three clinical investigator sites and one sponsor site between January and February 2015. The Integrated inspection report of the inspections carried out was issued on 15 April 2015.
- The applicant submitted the responses to the CHMP list of outstanding issues on 18 June 2015.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 30 June 2015 (Annex 7).
- PRAC RMP Advice and assessment overview, adopted by PRAC on 9 July 2015 (Annex 8).
- During a teleconference of the Infectious Disease Working Party on 11 June 2015, experts were convened to address questions raised by the CHMP (Annex 9).
- During the meeting on 23 July 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zerbaxa.

2. Scientific discussion

2.1. Introduction

Problem statement

Complicated UTI (cUTI) constitutes a heterogeneous clinical entity that includes UTI in the presence of factors that predispose to persistent or relapsing infection, such as indwelling catheters, urinary obstruction, instrumentation of the urinary tract, or other functional or anatomical abnormalities of the urogenital tract, and may occur in the lower or upper urinary tract. Pyelonephritis, a subset of cUTI, is an infection of one or both kidneys that can occur in patients with or without functional or anatomic abnormalities of the urinary tract. Complicated UTIs are a frequent cause of hospitalisation and a common health-care associated complication. Gram-negative organisms account for approximately 60% to 80% of complicated and nosocomial UTIs; the most common uropathogens are *E. coli*, *Klebsiella* spp, *Pseudomonas* spp, *Proteus* spp, *Enterobacter* spp, and *Citrobacter* spp.

Successful treatment of cUTIs has become increasingly more challenging because of rising rates of antimicrobial resistance among these pathogens. Indeed, the majority of pathogens responsible for healthcare-associated cUTIs, including catheter-related infections, are now commonly resistant to multiple antimicrobial agents highlighting the need for development of new antibacterial agents.

Intra-abdominal infections (IAIs) include a wide spectrum of pathological conditions, ranging from uncomplicated appendicitis to fecal peritonitis. In complicated IAI (cIAI) the infection progresses beyond a singularly affected organ and causes either localized peritonitis (intra-abdominal abscesses) or diffuse peritonitis. This peritoneal contamination may result from spontaneous perforation (e.g. appendicitis, perforated ulcer or diverticulitis), surgical intervention, or trauma.

Effective management of these infections requires a combination of early diagnosis, appropriate surgical intervention, and empiric, broad-spectrum antimicrobial therapy. Overall mortality rates in cIAIs remain as high as 25% with subjects who develop tertiary peritonitis experiencing even greater rates of mortality. Complicated IAIs are common infections encountered in general surgery and have been estimated to be responsible for 20% of all severe sepsis episodes in the intensive care unit. The severity of the underlying disease and inappropriate antimicrobial therapy, due in part to increased antimicrobial resistance, significantly contributes to the mortality rate observed in cIAIs.

Pathogens most commonly encountered in cIAI are *Escherichia coli*, other common *Enterobacteriaceae* (e.g. Proteus, Klebsiella spp.), *Pseudomonas aeruginosa* and *Bacteroides fragilis*. Second or third generation cephalosporins in combination with metronidazole, extended-spectrum penicillin/beta (β)-lactamase inhibitors (BLIs) and carbapenems are commonly used for the treatment of cIAI. However,

increasing resistance to commonly prescribed antimicrobial agents is a recognised serious global problem. Indeed, susceptibility data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) indicate that 18% of *E. coli* collected worldwide expressed extended spectrum beta-lactamases (ESBLs) from 2005 to 2007, while the number of ESBL-positive *Klebsiella pneumoniae* significantly increased from 13.3% in 2002 to 30.9% in 2007. In addition, *P. aeruginosa* resistance in cIAI remains a problem.

About the product

Ceftolozane is a semisynthetic, parenteral antibiotic of the cephalosporin class. Ceftolozane as the sulfate has a molecular formula of $C_{23}H_{31}N_{12}O_8S_2+\bullet HSO_4-$ and the molecular weight is 764.77 g/mol.

Like other members of the cephalosporin class, ceftolozane exerts its bactericidal activity by inhibiting essential penicillin-binding proteins (PBPs), resulting in inhibition of cell wall synthesis and subsequent cell death.

Tazobactam acid is a penicillanic acid sulfone derivative which can inhibit many bacterial class A - and some class C - β-lactamases. Tazobactam can potentially protect ceftolozane from hydrolysis by some beta-lactamases, broadening its spectrum to include most ESBL-producing *E. coli, K. pneumoniae* and other *Enterobacteriaceae*.

Final indications:

Zerbaxa is indicated for the treatment of the following infections in adults (see section 5.1):

- Complicated intra-abdominal infections (see section 4.4)
- Acute pyelonephritis;
- Complicated urinary tract infections (see section 4.4).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

(Acute pyelonephritis, although subset of cUTI, has been separated as indication, whilst data limitations for cUTI and cIAI are stated in section 4.4 SmPC)

Proposed (final) posology:

The recommended intravenous dose regimen for patients with creatinine clearance > 50 mL/min is shown by infection type in Table 1.

Table 1: Intravenous dose of Zerbaxa by type of infection in patients with creatinine clearance > 50 mL/min

Type of infection	Dose	Frequency	Infusion time	Duration of treatment
Complicated intra-abdominal infection*	1 g ceftolozane / 0.5 g tazobactam	Every 8 hours	1 hour	4-14 days
Complicated urinary tract infection Acute pyelonephritis	1 g ceftolozane / 0.5 g tazobactam	Every 8 hours	1 hour	7 days

*To be used in combination with metronidazole when anaerobic pathogens are suspected.

Special populations

Elderly (≥ 65 years of age)

No dose adjustment is necessary for the elderly based on age alone (see section 5.2).

Renal impairment

In patients with mild renal impairment (estimated creatinine clearance [CrCL] > 50 mL/min), no dose adjustment is necessary, see section 5.2).

In patients with moderate or severe renal impairment, and in patients with end stage renal disease on haemodialysis, the dose should be adjusted as listed in Table 2 (see sections 5.1 and 6.6).

Table 2: Intravenous dose of ceftolozane/tazobactam in patients with creatinine clearance ≤ 50 mL/min

Estimated CrCL (mL/min)*	Recommended dose regimen for Zerbaxa (ceftolozane/tazobactam)**
30 to 50	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours
15 to 29	250 mg ceftolozane / 125 mg tazobactam intravenously every 8 hours
End stage renal disease on haemodialysis	A single loading dose of 500 mg ceftolozane / 250 mg tazobactam followed after 8 hours by a 100 mg ceftolozane / 50 mg tazobactam maintenance dose administered every 8 hours for the remainder of the treatment period (on haemodialysis days, the dose should be administered at the earliest possible time following completion of haemodialysis)

*CrCL estimated using Cockcroft-Gault formula
**All doses of Zerbaxa are administered intravenously over 1 hour and are recommended for all indications. The duration of treatment should follow the recommendations in Table 1.

Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of ceftolozane/tazobactam in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Zerbaxa is for intravenous infusion.

The infusion time is 1 hour for 1 g / 0.5 g of Zerbaxa.

Precautions to be taken before handling or administering the product

See section 6.2 for incompatibilities.

See section 6.6 for instructions on reconstitution and dilution of the medicinal product before administration.

2.2. Quality aspects

2.2.1. Introduction

The finished product is a fixed combination powder for concentrate for solution for infusion containing 1 g ceftolozane and 0.5 g tazobactam (as sodium salt) as active substances.

Other ingredients are: sodium chloride, arginine and anhydrous citric acid, as described in section 6.1 of the SmPC.

At the time of administration, the contents of the vial are reconstituted using 10 ml sterile Water for Injection or 0.9 % Sodium Chloride Injection followed by further dilution in an infusion bag of 100 ml of 0.9 % Sodium Chloride Injection or 5 % glucose Injection.

Zerbaxa 1 g / 0.5 g powder for concentrate for solution for infusion is available in 20 ml type I glass vial, closed with a bromobutyl rubber stopper and sealed with an aluminium seal and plastic flip off cap, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Ceftolozane

General information

The chemical name of the active substance ceftolozane is (6R,7R)-3-[[3-amino-4-(2-aminoethyl-carbamoylamino)-2-methylpyrazol-1-ium-1yl]methyl]-7-[[(2Z)-2-(5-amino-1,2,3 -thiadiazol-3-yl)-2-(2-carbocypropan-2-yloxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; hydrogen sulfate, corresponding to the molecular formula $C_{23}H_{31}N_{12}O_8S_2^+.HSO_4^-$ and has a relative molecular mass 764.77 g/mol. The active substance has the following structure:

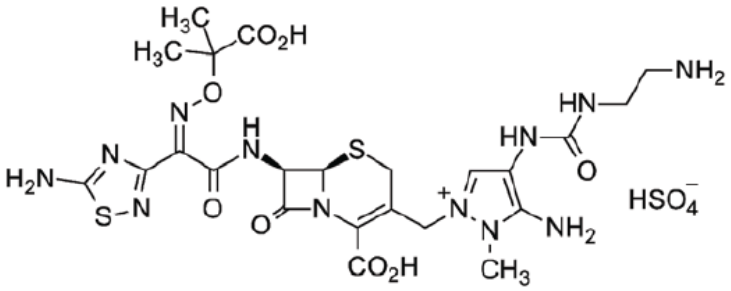


Figure 1

The structure of the active substance has been confirmed by elemental analysis, UV, ^{1}H- and ^{13}C-NMR, IR, MS and XRD, all of which support the chemical structure. The water and sulfate ion content were evaluated using Karl Fisher and ion chromatography methods respectively.

The absolute configuration of ceftolozane sulfate stereocentres at positions 6 and 7 and the geometry of the oxime moiety have been determined respectively to be in *6R, 7R* configuration and the C=N of the oxime moiety in Z configuration. The *6R, 7R* configuration and the Z configuration of C=N in the oxime moiety were evaluated and are controlled in the starting materials.

Ceftolozane appears as a white to off white hygroscopic powder. The pKa values are 9.3, 3.2 and 1.9. The solubility in water at 25°C is 27 mg/ml, 35.0 mg/ml at pH 2.5 (0.05M sodium perchlorate) and 32.3mg/ml at pH 4.0 (0.05M sodium perchlorate). A 2% aqueous solution has a pH of 1.9.

The active substance is mostly amorphous, containing some degree of crystallinity. No changes in XPRD spectra were observed following storage at -20°C (18 months), 5°C (18 months), or 25°C (6 months). The polymorphic form was not considered a critical attribute on the basis that the substance is dissolved during finished product manufacture.

Manufacture, characterisation and process controls

Ceftolozane sulfate is manufactured from 3 starting materials in 4 stages, which are comprised of a number of sub-stages. Two manufacturing sites are involved in the production of the active substance. The starting materials (SMs) are well characterised and are controlled by acceptable specifications. Sufficient information about their source and synthesis has been presented. A comprehensive discussion of the potential impurities that may be present in the starting material has been provided. Purging factors have been calculated and it has been demonstrated that the synthetic route downstream adequately purges any possible contaminants. The fate of Class 2 and Class 3 residual solvents has been satisfactorily discussed and where necessary they are appropriately controlled. A

thorough discussion of potential GTIs in the described synthesis was also provided. Given the controls applied to the synthesis of SMs, their purity, and the capability of the process to purge impurities, the proposed SMs are considered acceptable and in line with the principles of ICH Q11 and the EMA reflection paper on drug substance starting materials. No reworking is proposed for ceftolozane or any intermediates, however any material not meeting the acceptance criteria will be re-processed in line with ICH Q7A.

The same synthetic route was used for the manufacture of active substance for all clinical trials, registration stability studies and non-clinical studies. However, additional development work was carried out using traditional single variable (one variable at a time) experiments and multivariate statistical (Design of Experiments) studies to optimize the process and controls for each stage of the synthesis. Critical Process Parameters (CPPs) have been determined for each sub-stage and suitable in-process controls are applied during the synthesis. The specifications and control methods for intermediate products and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Ceftolozane sulfate is packaged in double polyamide / polyethylene bags heat sealed under vacuum, placed inside a four layered LDPE/nylon/aluminium/polyester outer bag and stored inside a carton box. The packaging material complies with EU Regulations 10/2011 and 202/2014.

Specification

The active substance specification includes tests for: appearance (visual), identification (IR, HPLC), counter ion sulfate (IC), colour of solution (Ph. Eur.), water content (KF), optical rotation (polarimetry), assay (HPLC), related substances (HPLC), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), isopropylic alcohol (GC), residual trifluoroacetic acid (IC), microbial limits (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). The tests for pH, clarity of solution, crystallinity, arsenic, and residual solvents other than isopropylic alcohol were omitted from the drug substance specifications. The control for pH was omitted on the basis that sulphuric acid content is controlled through the counter ion sulfate test. The clarity of solution and crystallinity are not considered CQAs. The test for arsenic was omitted because it is not used in the manufacturing process. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided. The proposed specification and limits are acceptable.

Batch analysis results for nine pilot scale and one commercial scale batches manufactured at the proposed site using the commercial process were presented. Supportive batch analysis data from nine development batches used in the manufacture of clinical, non-clinical, process development were also provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot batches of active substance from the proposed manufacturer stored in the intended commercial package for 12 months under long term conditions at at -20 °C and 5 ±3 °C, and for six months under accelerated conditions at 25 °C / 60 % RH according to the ICH guidelines were provided.

The following parameters were tested: for appearance, colour of solution, water content, optical rotation, potency, assay, microbial limits, bacterial endotoxins, specified impurities, total impurities, purity and unspecified impurities. The analytical procedures used were the proposed for release testing and were shown to be stability indicating.

Data were provided for up to 12 months at -20 °C, and 5 °C. All batches showed compliance with the specification at all time points and the statistical analysis of the data demonstrates no trending is expected. Data obtained at 25 °C / 65 %RH were not reported on the basis that the proposed storage condition was -20°C. This has been accepted considering the stability profile of the active substance.

Forced degradation studies for ceftolozane sulfate was performed during method validation. Conditions of hydrolysis (acid, base), oxidation, heat, light and humidity were tested. The degradation pathways were presented. A hydrolysis product typically found in cephalosporin products is the main solution degradant. Degradation was more prominent under conditions of base hydrolysis.

Based upon known photosensitivity of the ceftolozane the omission of photostability testing on the active substance was accepted. It is noted that the secondary container of the active substance includes an aluminium layer that protects the substance from light during storage at -20 °C.

Based on the overall data and justifications the proposed retest period of 12 months under storage at -20°C is acceptable.

Tazobactam sodium

General information

The chemical name of the active substance tazobactam sodium is sodium (2S,3S,5R)-3-methyl-7-oxy -3-(1H-1,2,3-trizol-1-ylmethyl)-4-thia-1-azabicyclo-[3.2.0] heptane-2-carboxylate-4,4-dioxide, corresponding to the molecular formula $C_{10}H_{11}N_4N_aO_5S$ and has a relative molecular mass 322.28 g/mol. The active substance has the following structure:

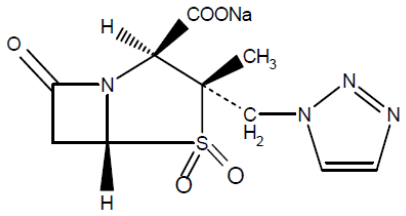


Figure 2

The structure of the active substance has been confirmed by elemental analysis, IR, UV, 1H-NMR, 13C-NMR, MS and thermal analysis, all of which support the chemical structure.

Tazobactam sodium appears as a white to off white very hygroscopic powder. It is freely soluble in water and slightly soluble in ethanol and acetone. An aqueous solution has a pH of 5.0 to 7.0. The substance's has a pKa of 2.6.

The substance is manufactured as a single stereoisomer. The stereochemistry is determined by the stereochemistry of the starting material and a stereospecific reaction. Polymorphism was not observed.

Manufacture, characterisation and process controls

Tazobactam sodium is manufactured in 10 steps from well-defined starting materials. Detailed information on the manufacturing of the active substance and tazobactam acid has been provided in the restricted part of the ASMF and it was considered satisfactory.

Tazobactam sodium is manufactured as a lyophilised sterile active substance. Tazobactam sodium is sterilised by filtration, lyophilisation, blending and aseptic filling into the proposed packaging. The sterilisation method was selected based on the heat sensitivity of the active substance. No catalysts

and no Class 1 solvents are used in the synthesis of the active substance tazobactam sodium. Reprocessing is not foreseen in the process. Acceptable specifications for starting materials intermediates and reagents were provided. The critical steps were identified as dissolution, filtration, loading, freezing, drying, end point of drying and yield, and sufficient in process controls are in place.

The characterisation of the active substance and its impurities are in accordance with the relevant EU guidelines. The carry-over of impurities, including genotoxic impurities, and residual solvents has been satisfactorily evaluated. One of the impurities is a degradation product. The impurities formed during the synthesis of tazobactam acid have been adequately characterised, and their origin has been specified.

The manufacturing process has been successfully validated using four consecutive commercial scale batches however the data provided.

Tazobactam acid container closure system has been adequately described and a declaration of compliance with 2002/72/EC was provided.

Tazobactam sodium is stored in aluminium tins, closed with aluminium caps and sealed with rubber rims. The tins are wrapped in double sterile polyethylene bags and placed inside cardboard boxes. Declaration of compliance with the relevant EU directives, including 2011/10/EEC has been provided.

Specification

The active substance specification includes tests for: appearance (visual), identification (IR, HPLC), counter ion sodium (Ph. Eur.), colour and clarity of solution (Ph. Eur.), visible foreign and particulate matter (Ph. Eur.), pH (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (KF), optical rotation (Ph. Eur.), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information on the reference standards has been provided. The proposed specification and limits are acceptable.

Batch analysis results for three commercial scale batches manufactured at the proposed site using the commercial process were presented. Analyses were done according to the proposed specifications and all data were compliant and consistent from batch to batch.

Stability

Stability data on three consecutive commercial scale batches of the sterile active substance from the proposed manufacturer stored in the intended commercial package for 30 months under long term stability studies (25 °C/60% RH), and for six months under accelerated conditions at 40 °C/75% RH according to the ICH guidelines were provided.

The following parameters were tested: appearance, IR spectrum, optical rotation, water, pH, clarity and colour of solution, related substances, assay, sterility, bacterial endotoxins and particulate matter. The analytical procedures used were the proposed for release testing and were shown to be stability indicating.

All results were well within the specifications. No significant changes occurred under any of the two storage conditions at any time point.

Forced degradation studies were performed in order to confirm the specificity of the HPLC method and to provide information about potential degradation pathways and degradation products. The results

showed that degradation increased under heating conditions, and less significantly during the light testing. After addition of acid and alkali, degradation is more prominent. At oxidative conditions degradation is less and slower.

Based on the overall data and justifications the proposed retest period of 36 months with no special storage conditions is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Zerbaxa 1g/0.5g powder for concentrate for solution for infusion, is presented as a combination of two sterile powders in a single vial, intended for reconstitution and infusion.

The aim of pharmaceutical development was to manufacture a suitable sterile formulation for infusion with a short re-constitution time, a physiologically relevant pH, sufficient potency, purity and stability. The Quality Target Product Profile (QTPP) was determined as an i.v. formulation able to provide a dose of 1000mg ceftolozane and 500 mg tazobactam, being stable and meeting the specification and the relevant Pharmacopoeia requirements.

The product is manufactured by sequential aseptic filling of the ceftolozane, which is an intermediate product (DPI), and addition of sterile tazobactam sodium. The ceftolozane DPI consists of ceftolozane sulfate, and the excipients citric acid, sodium chloride and L-Arginine.

Ceftolozane DPI physicochemical properties possibly relevant to the finished product critical quality attributes (CQA) and manufacturing are bulk untapped and tapped density, particle size distribution and hygroscopicity. The same physicochemical properties are relevant for tazobactam sodium bulk powder. The effect of DPI particle size and tazobactam sodium particle size on reconstitution time is minimal due to the high solubility of all components. Water content is controlled in the specification of tazobactam sodium. The effect of ceftolozane DPI hygroscopicity on the finished product water content was also evaluated. For the ceftolozane/tazobactam drug product, the manufacturing process controls mitigate the potential influence of these physicochemical properties on the CQAs. After filling of both powders into the vials, the vials are overlaid with nitrogen to provide a low-humidity, inert environment.

It has been demonstrated that no changes in polymorphic form of ceftolozane occur throughout finished product manufacture or storage.

The proposed potency adjustment of ceftolozane is acceptable.

As a product intended for intravenous use, properties like particulate matter, sterility, endotoxin limit, pH, and osmolality are important for physiological compatibility. Particulate matter and sterility/endotoxin levels are controlled throughout the entire aseptic manufacturing process. The product pH is controlled to approximately pH 6 as IPC and at product release specification, in order to provide physiological comfort, and, at the same time, assuring adequate stability for the two substances. The tonicity of this product following reconstitution and dilution for infusion as per the SmPC (section 6.6) has been evaluated and is deemed acceptable for peripheral administration.

The excipients and packaging components are well known and used in intravenous products. The compatibility of ceftolozane with the proposed excipients was evaluated and is supported by long term stability data. The compatibility of DPI and tazobactam sodium was established in long-term stability studies (36 month) for a blended product, made for Phase 2 and Phase 3 clinical trials.

Sodium chloride was selected as the sole stabilising agent, based on the lower total impurity level compared with other stabiliser tested. L-arginine showed also lower levels of impurities and a more stable pH compared with other alkalising agent and was therefore selected in the final formulation. Citric acid has been included in the formulation in order to control any degradation /sub-visible particulate formation due metal ions that may be introduced into the product from IV diluents. The choice of excipients has been adequately justified. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The formulations used during the early clinical development were presented; the proposed commercial formulation is identical in composition to the clinical product.

The finished drug product critical quality attributes (CQAs) are appearance, potency, identity, purity, moisture, reconstitution time, colour and clarity of solution, pH, content uniformity, particulate matter, sterility and endotoxins. The manufacturing process of the product consists of two main parts: i) the manufacture of ceftolozane DPI and ii) the aseptic filling of ceftolozane DPI and sterile tazobactam in vials. During the development of the manufacturing process a criticality assessment was conducted for the two manufacturing stages with regard to their direct impact on the product CQAs, based on knowledge of the ceftolozane sulfate and ceftolozane DPI properties, and prior knowledge. The CQAs that are affected by each one of the two main manufacturing stages were defined and the process parameters of each stage were further investigated through a series development studies. The different steps of the process were optimised and the studies resulted in establishing the critical process parameters for each step of the process as well as relevant holding times.

The clinical phase III product was manufactured using a blend and fill process, whereas the proposed commercial process is a co-fill. This was assessed further and pharmaceutical equivalence of the phase III product and proposed commercial process was shown by the release data and stability data.

The compatibility of the finished product with the diluents proposed for administration was evaluated using one batch of the finished product to assess the stability of the reconstitute and diluted product in the intravenous bag. The product was reconstituted in sterile water for injection or 0.9 % sodium chloride for injection and diluted in 0.9 % sodium chloride for infusion or 5% glucose solution for infusion. Data has been provided for the diluted product stored for up to 48 hours in ambient conditions or 14 days in a refrigerator. However it is noted that no analysis of microbial contamination was performed during the trials. Given the SmPC states that dilution should be performed in aseptic conditions and used immediately, it is considered that the compatibility and microbial data provided adequately support the proposed dilution and storage instructions (section 6.3).

Zerbaxa 1g/0.5g powder for concentrate for solution for infusion, is packaged in a 20 ml type I clear glass vial, closed with a bromobutyl rubber stopper sealed with an aluminium seal and plastic flip off cap. The material complies with Ph. Eur. and EC requirements. The container closures system is appropriate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 2 main stages: the manufacture of ceftolozane DPI and the manufacture of ceftolozane/tazobactam finished product. The first stage comprises five steps: compounding, filtration, aseptic lyophilisation, aseptic grinding/sieving and, aseptic packaging. The second stage comprises six steps: aseptic filling, Aseptic stoppering, Crimping, visual inspection and sampling, labelling and, packaging.

The critical steps in the ceftolozane DPI manufacturing stage and in the final product manufacturing process were identified. Acceptance criteria for the critical manufacturing process parameters were specified.

The in-process controls are adequate for this type of manufacturing process and the particular pharmaceutical form.

The proposed manufacturing process for the finished product includes steps is considered by to be non-standard process (aseptic processing, lyophilisation) as per the guideline on process validation.

The manufacturing process has been validated using four consecutive commercial scale batches manufactured by the proposed. All the results met the release acceptance criteria. The manufacturing process has been satisfactorily validated.

Product specification

The finished product release and shelf specification include appropriate tests for this kind of dosage form: appearance (visual), identity of both substances (UV, HPLC), constituted solution in water and in 0.9% sodium chloride (Ph. Eur.), colour of solution (Ph. Eur.), reconstitution time in water and in 0.9% sodium chloride, pH of reconstituted solution (pH-meter), water content (Ph. Eur.), potency of both substances (HPLC), related substances (HPLC), container closure integrity (vacuum), content uniformity (Ph. Eur.), particulate matter (Ph. Eur.), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.). The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Full details of the reference standards used were provided. The proposed specification, methods and limits are appropriate for this pharmaceutical form.

Batch analysis data for three commercial scale batches manufactured by the proposed manufacturer have been presented. The batches were analysed according to the proposed finished product specifications and showed good compliance for all parameters. In addition batch analysis data for all batches of finished product manufactured for during clinical development and commercialisation have been presented. All results are well within the specifications valid at the time of testing. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of four pilot scale primary registration batches of finished product batches stored under long term refrigerated conditions (5±3 °C) for 15 months and for 9 months under accelerated conditions at 25 ºC / 60% RH were provided. One batch was also stored in the inverted position in long term and accelerated conditions. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The batches were analysed according to the proposed shelf life specifications for the following parameters: appearance, water content, pH, potency, purity, related substances, particulate matter, colour of solution, constituted solution/reconstitution time and container closure integrity. The analytical methods were shown to be stability indicating. The data for all parameters showed good compliance for all parameters.

Additionally three batches of clinical trial material used in Phase 2 and Phase 3 pivotal clinical trials have been included as supportive data. The composition of these batches is identical to the proposed commercial product but they were manufactured by first blending the two sterile powders followed by

vial filling. The batches were placed on stability in long term (5 °C) and accelerated conditions (25°C / 60% RH) and analysed according to the proposed specifications. All data showed good compliance in long term and accelerated conditions up to time 36 months in both storage conditions.

Forced degradation studies were conducted with one pilot batch of the finished product, placed on stability in heat, humidity, basic, acidic, oxidative, and light stress conditions. The samples were evaluated for potency and impurities. The degradation observed in all conditions was consistent with the substances degradation pathways.

A photostability study was conducted with one pilot batch, according to ICH Q1B. No significant change was observed for the samples packaged in their market packaging, however the unlabelled vials exhibited a significant increase in one impurity (out of specification), confirming the photosensitive nature of the proposed product. An instruction to store in the original container in order to protect from light has been included in the SmPC (section 6.4).

Also based on the results of the compatibility studies (see *above "Description of the product and pharmaceutical development"*) the storage instruction regarding the reconstituted product in the SmPC (section 6.3) is justified.

Based on available stability data, the shelf-life of 30 months when stored at 5±3°C in the original package in order to protect from light, as stated in the SmPC (section 6.4) are acceptable.

Adventitious agents

No excipients of human or animal origin are used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of both active substances and the finished product has been presented in a satisfactory manner. Tazobactam sodium is manufactured as a sterile active substance by a validated process. The finished non standard manufacture has been validated as per the relevant guideline. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

GLP

Pivotal studies for safety pharmacology, general toxicity including reproductive toxicity studies were conducted in accordance with Good Laboratory Practice (GLP) principles. Toxicokinetic (TK) and some pharmacokinetic (PK) studies were also conducted according to GLP and while some other studies were not strictly GLP. These studies appeared to conform to adequate scientific standards of quality

2.3.2. Pharmacology

Primary pharmacodynamic studies

A series of in-vitro and in-vivo studies were conducted to determine the antibacterial activity of ceftolozane /tazobactam. See the clinical section 2.4.3. on Pharmacodynamics for a brief summary.

Secondary pharmacodynamic studies

Receptor/enzyme screens for ceftolozane at 766 µg/mL inhibited (by > 50%) binding to 16/130 targets assessed in a serum free in-vitro binding assay. Specifically, ceftolozane inhibited binding to histamine H3 (56%), opioid delta 2 (51%), opioid kappa 1 (57%), opioid mu (89%), purinergic P2Y (59%), sigma 1 (52%), cholecystokinin CCK1 (96%), and neurokinin NPY1 (62%) receptors. Ceftolozane also inhibited the activity of phosphodiesterases PDE10A2 (50%), PDE2A (66%), PDE3B (61%), PDE4A1A (55%), PDE5A1 (57%), as well as protein kinases Akt1 (84%) and MEK1 (100%) and the histone deacetylase SIRTUIN1.

Safety pharmacology programme

A core battery of GLP compliant safety pharmacology studies, as well as several additional non-GLP studies, has been conducted with ceftolozane (developmental process). Toxicokinetic parameters were not measured in the safety pharmacology studies, but were extrapolated from exposure data in pivotal toxicity studies conducted in rats and dogs.

Receptor/enzyme screens for ceftolozane at 766 µg/mL inhibited (by > 50%) binding to 16/130 targets assessed in a serum free in-vitro binding assay. A concentration of 766 µg/mL is approximately 13-fold greater than the mean clinical ceftolozane Cmax (~57 µg/mL). There were no effects in the hERG assay at concentrations of up to 1000 µM (~ 667 µg/mL), which is approximately 11.7-fold the clinical Cmax.

In a rat study in which animals were given IV doses of up to 1000 mg/kg, mean blood pressure transiently decreased by 8%, 11%, and 27% at 100, 320, and 1000 mg/kg, respectively. Heart rate decreased by 8%, 11%, and 22% at 100, 320, and 1000 mg/kg, respectively, at 1 minute post dose. In a telemetered dog study a rapid, transient increase in heart rate at 15 minutes post-dose was noted in one animal at 300 mg/kg; there was a 37% increase in heart rate vs. baseline. No statically significant effects on cardiovascular functioning were seen in rats or dogs following IV administration of ceftolozane at 100 mg/kg. The effects seen in these studies occurred at doses with estimated associated Cmax values of 728 to 2028 µg/mL for male rats and 793 µg/mL for male dogs, approximately 12.8- to 35.6-fold greater than the mean clinical Cmax. No ECG effects were noted at any dose. Given there were no effects seen on ECGs in this study and in the 4 week dog general

toxicology study and there are significant clinical data, the effects seen these safety pharmacology studies effects are unlikely to translate into the clinical setting.

No renal safety pharmacology studies were conducted with ceftolozane or tazobactam either alone or in combination. The applicant states that a renal safety pharmacology study with ceftolozane was not conducted based on the lack of adverse effects noted in rats and dogs following repeat administration for up to 28 days. The presence of hyaline droplets in the tubular epithelial cells of the renal cortex of rats and dogs (and associated increases in kidney weights in rats) following repeat IV administration was considered non-adverse up to a dose of 1000 mg/kg/day.

An independent, expert Pathology Working Group (PWG; comprised of four Board-certified pathologists with expertise in the evaluation of renal pathology) reviewed these renal changes in rats and dogs, to discuss the pathological interpretation of the studies, and provide expert guidance on the clinical relevance of these findings. The PWG concluded that the ceftolozane-related accumulation of hyaline droplets in the tubular epithelial cells of the renal cortex of rats and dogs was not adverse even up to a dose of 1000 mg/kg/day. This conclusion was based on the lack of toxicologically meaningful degeneration or necrosis present in affected renal tubules with no effects on renal function as determined by the absence of biologically relevant changes in BUN, creatinine, inorganic phosphorus or urine volume, as well as the absence of cellular/granular casts in the urine and clinical signs of systemic toxicity. In both the GLP 4-week rat and the dog studies with ceftolozane study and the combined 4-week rat study (ceftolozane or tazobactam), the NOAELs were set at 1000, 300 and 1000 mg/kg/day, respectively, as a result of the findings of the PWG. However in the final study reports the NOAELs were set at 100, 100 and 250/125 mg/kg/day respectively.

For the 4-week rat study (GLR050690) using the combined Cmax and AUC for both sexes at 100 mg/kg/day at week 4 (208.4 µg/mL and 217.25 µg•h/mL, respectively) the margins of safety over the clinical dose would be 0.6 for AUC and 3.6 Cmax (cIAI) and 0.5 for AUC and 3.6 for Cmax (UTI). For the 4-week dog study (GLR050729) using the combined Cmax and AUC for both sexes at 100 mg/kg/day at week 4 (258.1 µg/mL and 408.35 µg•h/mL, respectively) the margins of safety would be 1.2 for AUC and 4.5 Cmax (cIAI) and 0.9 for AUC and 4.5 for Cmax (UTI).

Given that hyaline droplets in the tubular epithelial cells of the renal cortex of rats and dogs were not shown to be associated with any other renal function/pathology findings and that even at the lower NOAELs stated in the final study reports suitable Cmax margins of exposure cover exist over the clinical Cmax and that the intended clinical dose of 1000 mg/500 mg per treatment for up to 14 days (i.e. short duration of dosing), the findings of these studies are unlikely to be a clinical safety concern. However the occurrence of hyaline droplets within the proximal tubular epithelium of the kidney represent lysosomes containing drug and membrane remnants, and so are considered a class-effect of cephalosporins. Clarification as to why the renal findings have not been included in the proposed SmPC is required.

Renal safety pharmacology studies should have been conducted with the ceftolozane and tazobactam combination. However given the stage of development and data available from the general toxicology studies, generating this specific data at this stage would not provide any additional value to the risk assessment of the ceftolozane/tazobactam combination.

In rats given single doses of 0, 68.9, 207, or 689 mg/kg by IV infusion, no neuropharmacological or toxicological signs (up to 24 hours post-dose) or effects on body temperature were seen at any dose. The 689 mg/kg dose had a projected mean Cmax 1397 µg/mL (i.e. 24.5-fold mean clinical Cmax).

Ceftolozane solutions did not induce histamine release from human WBC *in vitro* at concentrations ~52.6-fold clinical Cmax.

2.3.3. Pharmacokinetics

Following single and repeat-dose IV administration of ceftolozane to animals, pharmacokinetic analysis revealed t1/2 of 0.29 hour and 1 hour in rats and dogs, respectively, with rapid clearance and a relatively low Vd. Systemic exposure was dose proportional over a broad range of doses (10 to 1000 mg/kg/day) with no significant accumulation following repeat administration or any gender-related differences.

Three studies have been conducted in which the PK parameters of ceftolozane and tazobactam were determined following IV administration of each agent alone, or in combination at the 2:1 ratio proposed for clinical use. A single dose PK study was conducted in Beagle dogs. In addition, repeat-dose toxicokinetic (TK) data were collected during 14-Day and 28-Day toxicology studies in dogs and rats, respectively. Overall, these studies demonstrated that systemic exposure to either ceftolozane or tazobactam was similar whether these drugs were administered alone or in combination, suggesting no significant PK drug-drug interaction between ceftolozane and tazobactam. In general, there were relatively dose-proportionate increases in systemic exposure to ceftolozane and tazobactam over the dose ranges assessed, suggesting that ceftolozane and tazobactam have linear kinetics when administered together. Both ceftolozane and tazobactam were eliminated rapidly with short t1/2 (< 1.1 h) in both species.

The in-vitro protein binding of ceftolozane in serum from mice, rats, dogs and humans as well as in human plasma was low. Ceftolozane showed < 21% serum protein binding across species with human serum protein binding values ranging from 14.6% to 16.8%, slightly lower than human plasma values (16.3% to 20.8%).

The distribution of ^{14}C-labeled ceftolozane in blood, plasma, and tissues was determined in rats. The t1/2 for ^{14}C-labeled ceftolozane was 0.35 h in both plasma and blood. Five minutes after administration, the tissue-to-plasma concentration ratio of radioactivity was found to be highest in the kidney and urinary bladder with tissue to blood ratios of 3.05 and 2.36, respectively. Concentrations of radioactivity were at a maximum 5 minutes after administration. Tissue concentrations in the brain and pituitary were below detection limits. A total of 13 metabolites were observed across plasma, urine, faeces, bile and kidney homogenates of rats administered IV ^{14}C-ceftolozane. These metabolites were minor with each metabolite representing ≤5.1% of administered radioactivity and most accounting for approximately ≤1%.

Given the high distribution of ceftolozane to the kidney, the presence of metabolites for ceftolozane was also analysed in the supernatants of rat kidney homogenates following IV administration of ^{14}C-labeled ceftolozane. Ceftolozane and four unidentified metabolites (MH-1, MH-2, MH-7 and MH-11) were detected in the kidney at 5 and 15 minutes after administration; however, these metabolites were not seen between 2 and 96 hours post dose. Overall, ceftolozane accounted for 82%, 84.7% and 80% of the total radioactivity in the kidney at 2, 8 and 96 h post dose, while the four unidentified metabolites each accounted for 4.3% or less of the total radioactivity.

These results demonstrate minimal metabolism of ceftolozane following IV administration with most of the intact compound being excreted rapidly in the urine. Based on the low levels of metabolites detected in the biological matrices assessed (<10%), the structures of the metabolites do not require identification.

Thirteen P450 studies were conducted (inhibition and induction); 7 studies with ceftolozane, 4 studies with tazobactam and 2 studies with the tazobactam M1 metabolite. Ceftolozane, tazobactam, and tazobactam M1 demonstrated low potential for drug-drug interaction (DDIs) at clinically relevant concentrations *in vitro*. The applicant provided a satisfactory discussion of the drug-drug interaction *in*

vitro data in relation to the free unbound fraction. No potential to cause clinical DDIs involving the human transporters OATP1B1, OATP1B3, OCT1, OCT2, P-gp, BCRP and BSEP were noted in these studies. In addition no potential for ceftolozane to cause clinical DDIs involving the human MATE1, MATE2-K and MRP-2 transporters at clinically relevant blood concentrations was noted. Tazobactam inhibited the human OAT1 and OAT3 transporters *in vitro* with Ki values calculated at 117.7 and 146.7 µg/mL (approximately 8 to 10-fold greater than the free plasma Cmax value of 15.4 µg/mL), respectively. Based on these in-vitro findings, a clinical study was conducted to evaluate the potential of tazobactam to influence the pharmacokinetics of the OAT1/OAT3 probe substrate furosemide, which showed no relevant interaction at the intended clinical dose.

No PK drug-drug interactions were observed between ceftolozane and tazobactam following single or repeat IV administration to rats and dogs for up to 28 days.

2.3.4. Toxicology

Single dose toxicity

In single dose toxicology studies, ceftolozane was associated with decreased body weight in mice following a single IV administration at ≥1500 mg/kg. Convulsions and mortalities were seen at 2000 mg/kg. The effects noted at 2000 mg/kg were associated with estimated C_{max} and AUC values of 6740 µg/mL and 1710 µg•h/mL, respectively; approximately 118-fold greater than the mean clinical C_{max} and 3.6 to 5.0-fold greater than the mean clinical AUC. No deaths occurred when ceftolozane was administered as a single IV dose to rats up to 2000 mg/kg. A transient decrease in body weight was observed at ≥1000 mg/kg, which was associated with estimated C_{max} and AUC values of 1845 µg/mL and 1282 µg•h/mL, respectively; approximately 32-fold and 2.7 to 3.7-fold the clinical values.

Vomiting was observed in dogs following a single IV administration of ceftolozane ≥300 mg/kg with flushing of auricles/oral mucosa seen at ≥500 mg/kg. Additional clinical signs observed at 2000 mg/kg included prone position, decreased spontaneous motility, swelling of the head, dark purplish coloration of the skin, increased glutamate pyruvate transaminase activity, and decreased serum calcium levels in males. These findings are consistent with a C_{max} related, direct histamine-mediated mast cell activation reaction and an increase in plasma histamine levels was observed in dogs following a single IV administration of ceftolozane. The more severe effects noted in dogs at 2000 mg/kg were associated with estimated C_{max} and AUC values approximately 100-fold and 20 to 28-fold greater than the clinical ceftolozane values.

Repeat dose toxicity

Repeat dose toxicology studies were conducted in rats and dogs of up to 4 weeks in duration via the IV route of administration with either ceftolozane alone or ceftolozane in combination with tazobactam. Doses of up to 1000 mg/kg/day ceftolozane were given to animals. In the combined studies 0/0, 1000/0, 0/500, 100/50, 250/125, 1000/500 ceftolozane/tazobactam were given to rats and 0/0, 300/0, 0/150, 100/50, or 300/150 ceftolozane/tazobactam were given to the dogs.

In the pivotal GLP 4 week IV dog study (100, 300, and 1000 mg/kg/day) at 1000 mg/kg/day reversible decreases in red blood cell parameters, vomiting, flushing of the auricles/oral mucosa, swelling of the head, salivation, and lateral position (consistent with histamine related mast cell degranulation) effects were seen. The NOAEL for systemic toxicity was 300 mg/kg/day based on cephalosporin-induced histamine-related in-life signs. The clinical safety margins are considered to be adequate. These findings were not seen clinically.

Hyaline droplets (confirmed as secondary lysosomes by electron microscopy) were detected in proximal renal tubules of rats and dogs following once daily repeated IV administration of ceftolozane for 28 days at doses of 300 and 1000 mg/kg/day in both species. Corresponding increase in kidney weight was consistently observed at these doses in rats but not dogs. Rats appeared more sensitive to these effects than dogs, as did male rats compared to females. Hyaline droplets were detected in rats given ceftolozane at doses with lower systemic exposure (plasma AUC and C_{max} values) compared to dogs. These effects were associated with a slight dose response relationship in both species with the degree of hyaline droplets increasing from minimal at 300 mg/kg/day to minimal to moderate at 1000 mg/kg/day. In dogs, increasing the duration of IV administration of ceftolozane from 2 weeks to 4 weeks appeared to result in an increase in the incidence and degree of hyaline droplets suggesting that this renal change may increase with duration of dosing.

The hyaline droplets observed in proximal tubular cells in renal cortex in rats and dogs can be interpreted as the initial step towards the known dose related pathogeneses of renal accumulation, that, for some cephalosporins, eventually lead to degeneration of the renal tubular epithelium. For ceftolozane, however, no microscopic evidence of renal tubular degeneration or necrosis was detected and no relevant effect on renal function was noted as determined by biologically relevant changes in serum BUN, creatinine, inorganic phosphorus, or urine volume. Calculation of safety margins based on the highest dose level tested is therefore considered acceptable. A safety margin of approximately 10 (based on AUC levels), together with supportive clinical data, is sufficient to address the safety concerns associated with this known cephalosporin class effect.

Ceftolozane is not considered to have an immunotoxic potential, based on lack of consistent effects on lymph nodes or cells of the immune system in a popliteal lymph node assay in mice, and lack of toxic findings on the immune system in repeat-dose toxicity studies in rats and dogs. In early, non-GLP screening studies conducted with early ceftolozane lots, lymphoid follicular development were observed in mice and rats. These findings are, however, not considered ceftolozane related, but are most likely related to the presence of endotoxin in these early lots.

Caecal effects (increased cecum weight in the presence or absence of dilatation) were detected in rats at doses of 100 to 1000 mg/kg/day. Increased cecum weights with or without caecal dilatation following administration of antibiotics to rodents has been previously described. This effect is caused by a change in the intestinal flora and is not considered to be toxicologically relevant to humans.

No new effects or unexpected toxicities were observed when ceftolozane was administered in combination with tazobactam in a 2:1 ratio to rats compared to the individual agents. The findings observed with the combination were comparable to the individual agents with regard to both incidence and severity.

Genotoxicity

One in silico study, four screening genotoxicity studies, and eight pivotal GLP genotoxicity studies were conducted with ceftolozane either alone or in combination with tazobactam.

Ceftolozane was negative for structural alerts of mutagenicity using DEREK and Leadscope in silico analyses. Ceftolozane was negative for genotoxicity in a bacterial mutagenicity assay, a mammalian chromosomal aberration assay, a mouse micronucleus assay, and an in vivo/in vitro rat liver UDS assay. Ceftolozane was marginally positive (with a questionable concentration response relationship) in a mouse lymphoma mammalian mutagenicity assay up to 500 µg/mL. As a follow-up strategy for the positive MLA in vitro, the applicant has provided a negative in vivo micronucleus test in mice at systemic exposure higher than expected exposures in patients at therapeutic doses.

Ceftolozane in combination with tazobactam at a 2:1 ratio did not induce gene mutations in mouse lymphoma cells, did not cause numerical chromosome aberrations in CHO cells, and was not associated with an increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow of rats. Ceftolozane in combination with tazobactam was positive for structural chromosome aberrations in CHO cells at concentrations associated with cytotoxicity. The relevance of this finding is uncertain as each of the individual ceftolozane and tazobactam test articles were not clastogenic at similar concentrations.

Ceftolozane and tazobactam are intended to be used for short term administration (i.e. less than 14 days and for the treatment of life-threatening infections. Given that ceftolozane in combination with tazobactam at a 2:1 ratio did not induce gene mutations in mouse lymphoma cells and was not associated with an increase in the incidence of micronucleated polychromatic erythrocytes in the bone marrow of rats, the weight of evidence suggests that the positive result obtained with ceftolozane in combination with tazobactam in the in vitro Chinese hamster ovary cell chromosomal aberration assay (structural aberrations) is unlikely to impact clinical safety, especially as individually they were not positive when tested alone at similar concentrations in this assay.

Carcinogenicity

No carcinogenicity studies were conducted with ceftolozane alone or in combination with tazobactam based on the intended short duration of therapy (<14 days), a lack of structural alerts for mutagenicity in Deductive Estimation of Risk from Existing Knowledge (DEREK) and Leadscope in silico analyses, a largely negative genotoxicity package (see above) and the lack of proliferative changes in any organ or tissue in general toxicity studies conducted in rats and dogs for up to 28 days. In addition, both ceftolozane and tazobactam belong to classes of compounds (cephalosporin and BLI) that historically have lacked evidence of carcinogenic potential.

Reproduction Toxicity

Ceftolozane did not affect fertility/reproductive performance or embryo/fetal development following repeat IV administration to rodents at doses up to 1000 to 2000 mg/kg/day, respectively. In a pre- and postnatal development study, ceftolozane administered to F0 rats from gestation day 6 to lactation day 20 was associated with a significant decrease in auditory startle response in post natal day (PND) 60 rats at maternal doses of 300 and 1000 mg/kg/day (study number: CX.101.TX.012).

The NOAEL for neurobehavioral effects was identified as 100 mg/kg/day. No effects on auditory startle response were observed on PND25 or PND53 in neonatal rats directly administered ceftolozane/tazobactam SC from PND4 through PND31. However, due to different time windows of exposure in the two studies, potential clinical relevance of the observed findings following exposure during late stage pregnancy in rats cannot be excluded. This is adequately reflected in SmPC.

This combination is intended to be used in the controlled environment of a hospital for not more than 14 days (i.e. short duration of dosing), thus the reproductive data suitably supports this application. No reproductive studies were conducted with ceftolozane in combination with tazobactam based on the results observed with the individual compounds.

Local Tolerance

Intravenous administration of ceftolozane to rodents was associated with injection site erythema and oedema at 300 to 2000 mg/kg/day. In general, the findings were very slight to slight.

No injection site findings were reported in dogs administered with IV ceftolozane. A rabbit dermal irritation study was so conducted in which animals were exposed to 0.5 g ceftolozane dermally for 4 hours. Ceftolozane did not cause dermal irritation under the conditions of this study

Other toxicity studies

A phototoxicity toxicity study was conducted in Long Evans rats. Animals were given IV doses of 0, 100, 300, 1000 mg/kg/day once daily for 4 days. Ceftolozane was not phototoxic at doses up to 1000 mg/kg/day.

Ceftolozane showed no potential to haemolyse human red blood cells in vitro at concentrations up to and including 50,000 µg/mL.

The antigenicity of ceftolozane was assessed in a non-GLP study conducted in female BDF1 mice. Mice were sensitised with an IP injection of ceftolozane at 10 or 100 µg/animal mixed with aluminium (4 g/animal). A second sensitisation was performed 21 days after the first sensitisation. This study revealed a negative passive cutaneous anaphylaxis (PCA) against all challenge antigens in all groups. A test for active systemic anaphylaxis (ASA) and a passive cutaneous anaphylaxis (PCA) was conducted in male Hartley guinea pigs using a skin reaction test with Ceftolozane. Ceftolozane did not elicit positive skin reactions, suggesting that there was no antigenic potential related to delayed-type hypersensitivity. ASA and PCA reactions were negative in animals sensitised with ceftolozane alone. Animals sensitised to test article plus Freund's complete adjuvant (FCA) evidenced positive ASA and PCA reactions, suggesting that the test article has antigenic potential related to immediate-type hypersensitivity under intense sensitising conditions. Hypersensitivity was not generally observed clinically (in clinical trials). These data suitability support this application.

Related substances

The manufacturing process material (that was used in most of the non-clinical studies) was modified to a more robust "commercial process". This 28 day bridging toxicity study in rats was conducted with ceftolozane manufactured using the "development" and "commercial" processes to demonstrate comparability and qualify a new impurity generated as a result of the process change. No new toxicities were seen. Ceftolozane-related degradants/impurities P1 (CB-607,341), P2a (CB-607,365), P2b (CB-607,366), P2c (CB-607,256), P3 (CB-607,367), P4 (CB-607,368), P5 (CB-607, 255), P7 (CB-604,629), and P9 (CB-604,235) can be considered qualified. Based on the current draft (Step 3) ICH M7 Guidance document, "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk", no genotoxic impurities are present in drug substance or drug product above levels considered acceptable for the intended short-term (≤14 days) drug administration period for treatment of serious Gram-negative bacterial infections.

2.3.5. Ecotoxicity/environmental risk assessment

The logDow,7.4 value of Ceftolozane was below 4.5 (i.e. logDow,7.4 = -0.21). Therefore Ceftolozane was not identified as a persistent, bioaccumulative and toxic (PBT) or a very persistent and very bioaccumulative (vPvB) substance. The Phase I $PEC_{SURFACEWATER}$ of Ceftolozane (0.57 µg/L) exceeded the action limit of 0.01µg/L, triggering a Phase II environmental fate and effects assessment.

The non-clinical data in mammalian species show a lack of toxicity in developmental and reproductive toxicity studies, and so Ceftolozane is not expected to affect reproduction of fish or lower organisms. For that reason, a standard Phase II fate and effects assessment was performed.

The logDow,7.4 value of ceftolozane was below 3 (i.e. logDow,7.4 = -0.21) and there are no other alerts for bioaccumulation. Therefore, the risk for bioaccumulation was considered acceptable.

PEC/PNEC ratios did not exceed the relevant triggers, and the risk to the aquatic, sewage treatment plant and groundwater compartments was concluded to be low. The Koc (6.5 to 1804 L/kg) was <10,000 L/kg and it was concluded that exposure to the terrestrial compartment as a result of spreading of sludge on soil is low.

Ceftolozane was not readily biodegradable; the results of a water-sediment study demonstrate that ceftolozane and/or its metabolites significantly shift to the sediment indicating potential exposure of this compartment. The PNEC derived from the subsequently performed sediment effect study exceeds the $PEC_{SEDIMENT}$ indicating that this compartment is not endangered. As a result Tier B Terrestrial risk assessment studies were not conducted. It is agreed that these studies were not required and that is Ceftolozane is not expected to pose a risk to the environment.

Table 3 Summary of main study results

Substance (INN/Invented Name): Ceftolozane (CXA-101)					
CAS-number (if available):936111-69-2					
PBT screening		Result			**Conclusion**
Bioaccumulation potential log D_{ow}		-0.21			Potential PBT: No
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$ Refined F_{pen} = 0.00038	0.57	µg/L			> 0.01 threshold: Yes
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption Study # 499013, GLP	OECD 106	Sludge: K_{oc}: 6.5-12 L/kg (n=2) K_d: 2.7-5.1 L/kg (n=2) Soil: K_{oc}: 167-1804 L/kg (n=3) K_d: 3.12-29.6 L/kg (n=3)			K_{oc} og K_d for sludge is below the trigger for Tier B assessment, 10000 L/kg and 3700 L/kg, respectively. A terrestrial risk assessment was not considered in Tier B.
Ready Biodegradability Test Study # 499011, GLP	OECD 301	Not readily biodegradable. Ceftolozane showed no biodegradability overall.			28 day study
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Study # 499017	OECD 308	Swiss Lake system $DT_{50, water}$ = 1.5 days $DT_{50, whole\ system}$ = could not be calculated % shifting of applied radioactivity to sediment = 24-27% Schoonrewoerdsewiel system $DT_{50, water}$ = 1.7 days $DT_{50, whole\ system}$ = could not be calculated % shifting of applied radioactivity to sediment = 35-63%			Significant shift of ceftolozane and/or its metabolites to the sediment layer was observed. A sediment effect study needed to be conducted.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition *(Anabaena flos-aquae)* Study # 77791210, GLP	OECD 201	EC_{10}	14.7	µg/L	Cyanobacteria were chosen since ceftolozane is an antimicrobial agent.
Daphnia sp. Reproduction Test Study # 499008, GLP	OECD 211	NOEC	7400	µg/L	
Fish, Early Life Stage Toxicity Test/ *(Pimphales promelas)*	OECD 210	NOEC	7700	µg/L	

Study # 499010, GLP					
Activated Sludge, Respiration Inhibition Test Study # 499012, GLP	OECD 209	NOEC	430000	µg/L	
Phase IIb Effect studies					
Sediment dwelling organism Freshwater chironomid: *Chironomus riparius* Study # 501293, GLP	OECD 218	NOEC	1423	mg/kg	
Derived PNEC values for ceftolozane					
	NOEC	**AF**	**PNEC**		
$PNEC_{Surfacewater}$	EC_{10} Algal growth inhibition test (*Cyanophyta*)	10	1.47 µg/L		
$PNEC_{Microorganism}$	NOEC respiration inhibition	10	43000 µg/L		
$PNEC_{Groundwater}$	NOEC Daphnia reproduction test	10	740 µg/L		
$PNEC_{Sediment}$	NOEC Sediment dwelling organism	100	14.23 mg/kg wwt		

Phase IIa and IIb risk evaluation

Environmental compartment	PEC	PNEC (µg/L)	PEC/PNEC	Trigger value	Conclusion
Surfacewater	0.57 µg/L	1.47 µg/L	0.39	1	No risk
Sewage water	0.57 µg/L	43000 µg/L	0.00001	0.1	No risk
Groundwater	0.14[1] µg/L	740 µg/L	0.0002	1	No risk
Sediment	22.7 µg/kg	14230 µg/kg	0.002	1	No risk

[1]: $PEC_{groundwater} = 0.25 \times PEC_{surfacewater}$

Substance (INN/Invented Name): Tazobactam			
CAS-number (if available): 89785-84-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential log $D_{ow7.4}$	?	-0.63	Potential PBT: No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ Refined F_{pen} = 0.00038	0.285	µg/L	> 0.01 threshold: Yes
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption Study # 499004, GLP	OECD 106	Sludge: K_{oc}: 0.8-3.0 L/kg (n=2) K_d: 0.31-1.34 L/kg (n=2) Soil: K_{oc}: 3.8-7.5 L/kg (n=3) K_d: 0.94-1.87 L/kg (n=3)	K_{oc} og K_d for sludge is below the trigger for Tier B assessment, 10000 L/kg and 3700 L/kg, respectively. A terrestrial risk assessment was not considered in Tier B.
Ready Biodegradability Test Study # 499002, GLP	OECD 301	Not readily biodegradable. Tazobactam was 2-10% overall biodegradable.	28 day study
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Study # 499007, GLP	OECD 308	Swiss Lake system $DT_{50, water}$ = 11.3 days $DT_{50, whole\ system}$ = 12 days Shifting to sediment = 7% Schoonrewoerdsewiel system $DT_{50, water}$ = 4.5 days	No significant shift of tazobactam to the sediment layer was observed.

		$DT_{50,\ whole\ system}$ = 5 days Shifting to sediment = 5%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition *(Anabaena flos-aquae)* Study # 77801210, GLP	OECD 201	EC_{10}	399	µg/L	Cyanobacteria were chosen since tazobactam in combination with ceftolozane is an antimicrobial agent. NOEC was not determined (<74.4 µg/L)
Daphnia sp. Reproduction Test Study # 498999, GLP	OECD 211	NOEC	8600	µg/L	
Fish, Early Life Stage Toxicity Test/ *(Pimphales promelas)* Study # 499001, GLP	OECD 210	NOEC	9500	µg/L	
Activated Sludge, Respiration Inhibition Test Study # 499003, GLP	OECD 209	NOEC	915000	µg/L	
Derived PNEC values for tazobactam					
	NOEC	**AF**	**PNEC (µg/L)**		
$PNEC_{Surfacewater}$	EC_{10} Algal growth inhibition test (*Cyanophyta*)	10	39.9		
$PNEC_{Microorganism}$	NOEC respiration inhibition	10	91500		
$PNEC_{Groundwater}$	NOEC Daphnia reproduction test	10	860		

Phase IIa risk evaluation

Environmental compartment	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC	Trigger value	Conclusion
Surfacewater	0.285	39.9	0.007	1	No risk. The use of EC_{10} is discussed below.
Sewage water	0.285	91500	0.000003	0.1	No risk
Groundwater	0.071[1]	860	0.00008	1	No risk

2.3.6. Discussion on non-clinical aspects

Studies evaluating the pharmacokinetics of ceftolozane alone, or in combination with tazobactam, were conducted in mice, rats and dogs following single and multiple iv doses.

Ceftolozane demonstrated dose-proportional PK following single and once daily repeat iv dose administration. There were no consistent and significant gender differences noted. Ceftolozane is rapidly distributed to tissues in rat, with highest levels detected in kidneys and urinary bladder. Upon repeated dosing, accumulation of ceftolozane in kidneys was observed across species. Plasma protein binding and transfer into blood cells is low for ceftolozane. Metabolism following iv administration is minimal, and excretion predominantly via the renal route.

Tazobactam exhibited an approximate dose proportional increase in both C_{max} and AUC following iv dose administration in combination with ceftolozane to rats and dogs. No consistent gender related differences were observed. Tazobactam is widely distributed into tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, and bile. Mean tissue concentrations are however lower than in plasma. Distribution into cerebrospinal fluid is low in subjects with non-inflamed meninges. Tazobactam crosses the

placenta in rats, but concentrations in the foetus are ≤ 10% of maternal plasma. Excretion in human milk has not been studied. Warnings have been included in section 4.6 of the proposed SmPC.

Tazobactam exhibits low plasma protein binding and is metabolized to a single major metabolite, M1, which lacks pharmacologic activity. Elimination of both tazobactam and the M1 metabolite is known to occur primarily by renal excretion.

Administration of ceftolozane and tazobactam in combination to rats and dogs did not alter the PK of either ceftolozane or tazobactam, as compared to the PK of each of the compounds when administered independently.

The toxicological potential of ceftolozane, both alone and in combination with tazobactam, has been characterized in studies of single- and repeat-dose toxicity, *in vitro* and *in vivo* genotoxicity, reproduction toxicity (including juvenile toxicity), antigenicity and phototoxicity. Further, studies to qualify the proposed impurity specifications have been conducted.

All pivotal studies with ceftolozane alone and in combination with tazobactam were conducted in accordance with GLP regulations. All *in vivo* toxicity studies used the intended clinical route of administration (iv). Although a 60-minute infusion three times daily is used clinically, all but one dog repeat-dose toxicity study (in dogs) used bolus administration once daily to assess the potential for C_{max}-related effects, and to minimise stress-related findings. Further, once daily administration to animals provided daily exposures in excess of human exposure at the intended clinical dose. One study conducted in dogs used twice daily administration by 15-minute iv infusion. No mortalities occurred when ceftolozane was administered as a single iv dose to rats or dogs up to 2000 mg/kg. A transient decrease in body weight was observed in rats at doses ≥1000 mg/kg. The more severe effects were noted in dogs at a dose of 2000 mg/kg, including vomiting, flushing of auricles/oral mucosa, swelling of the head, prone position, decreased spontaneous motility, and dark purplish coloration of the skin. The findings in dogs are consistent with a histamine-related mast cell degranulation effect, a known class-related effect of cephalosporins in dogs. Tazobactam-related effects in male dogs following single iv administrations include haematuria, vomiting, tremors, dry nose, shaking while breathing, conjunctival injection, reddening of skin, submucosal red spots or ecchymosis in the bladder, and decreased food consumption.

No new effects or unexpected toxicities were observed in animals when ceftolozane and tazobactam were co-administered for 2 to 4 weeks. Non-adverse, reversible changes evident in the kidney and liver were consistent with findings noted in studies with either compound alone.

The genotoxic potential of ceftolozane was evaluated in a number of *in vitro* and *in vivo* studies, including *in silico*, Ames test, mammalian chromosomal aberration, mouse lymphoma mammalian cell gene mutation assay (MLA), CHO mammalian cell HPRT gene mutation, rodent micronucleus, and *in vivo* rat liver unscheduled DNA synthesis (UDS). Tazobactam is a well-known substance devoid of a genotoxic potential. Ceftolozane was positive in the MLA *in vitro* when tested alone, and in the chromosomal aberration test *in vitro* when tested in combination with tazobactam. In view of otherwise negative *in vitro* and *in vivo* data (negative in silico data from two different systems, negative Ames test, negative findings in subsequent *in vitro* and *in vivo* studies with ceftolozane alone and in combination with tazobactam) at adequate exposure levels, and provided that the extrapolated exposure data are considered acceptable, the positive findings in MLA with ceftolozane and in the chromosomal aberration test with ceftolozane/tazobactam are considered of low clinical relevance.

No carcinogenicity studies with ceftolozane alone or in combination with tazobactam have been conducted, which is considered acceptable, in view of intended short duration of therapy.

Ceftolozane administered to rats during pregnancy and lactation was associated with a decrease in auditory startle response in postnatal day (PND) 60 male pups at maternal doses of 300 and 1000 mg/kg/day. Peri/postnatal development was impaired (reduced pup weights, increase in stillbirths, increase in pup mortality) concurrent with maternal toxicity after intraperitoneal administration of tazobactam in the rat.

Ceftolozane/ tazobactam is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity. Carcinogenicity studies with ceftolozane/tazobactam have not been conducted.

Effects in non-clinical studies were observed at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview

Clinical studies with pharmacokinetic data are listed below:

Table 4: Listing of clinical studies with pharmacokinetic data

Study ID (study start)	Objectives of the study	Study design	Treatment details	Subjects enrolled	Subjects receiving study drug	Subjects
CXA-101-01 (2008)	Safety, tolerability, PK	Phase I, single-centre, randomized, double-blind, placebo-controlled	Part I: Single dose ceftolozane 250, 500, 1000, 1500 and 2000 mg Part II: Multiple dose ceftolozane 500 mg q8h, 1000 mg q8h, or 1500 mg q12h for 10 days	64	48 ceftolozane	Healthy adult subjects
CXA-201-01 (2009)	Safety, tolerability, PK	Phase I, single-centre, randomized, double-blind, dose-escalation	Part I: Single dose ceftolozane 500, 1000, 2000 mg, single dose tazobactam 250, 500 1000 mg, single dose ceftolozane/ tazobactam 500/250, 1000/500, 2000/1000 mg Part II: Multiple dose ceftolozane 1000 mg q8h, or 1500 q12h, multiple dose tazobactam 500 mg q8h, or 1000 mg q12h, multiple dose ceftolozane/ tazobactam 1000/500 mg q8h, or 1500/750 mg q12h for 10 days	58	16 ceftolozane 16 tazo-bactam 26 ceftolozane /tazo-bactam	Healthy adult subjects
CXA-MD-11-07 (2011)	Safety, tolerability, PK	Phase I, randomized, double-blind, placebo-controlled	Multiple dose ceftolozane/ tazobactam 1000/500 mg q8h or 2000/1000 mg q8h for 10 days	16	12 ceftolozane /tazo-bactam	Healthy adult male subjects
CXA-ELF-10-03 (2010)	Safety, tolerability, PK, ELF penetration	Phase I, open label, randomized, comparator-controlled	Multiple dose ceftolozane/ tazobactam 1000/500 mg q8h or 4.5 g piperacillin/tazobactam	51	25 ceftolozane /tazo-bactam	Healthy adult subjects

			q8h, 3 doses		26 piperacillin /tazo-bactam	
CXA-QT-10-02 **(CUBI-RAS-006)** **(2010)**	Safety, QTc effect, PK	Phase I, randomized, double-blind, double-dummy, placebo- and active-controlled	Single dose ceftolozane/ tazobactam 1000/500 or 3000/1500 mg Positive control moxifloxacin 400 mg orally	52	51 ceftolozane /tazo-bactam	Healthy adult subjects
CXA-101-02 **(2009)**	Safety, tolerability, PK, effect of renal function	Phase I, open-label	Single dose ceftolozane 1000 mg	12	12 ceftolozane	Subjects with normal renal function or mild renal impairment
CXA-201-02 (CUBI-RAS-001) **(2009)**	Safety, tolerability, PK, effect of renal function	Phase I, open-label	Single dose ceftolozane/ tazobactam 1000/500 mg	24	24 ceftolozane /tazo-bactam	Subjects with normal renal function, or mild or moderate renal impairment
CXA-REN-11-01 **(2011)**	Safety, PK, effect of renal function	Phase I, open-label, prospective, multicentre	Severe renal impairment: Single dose ceftolozane/ tazobactam 1000/500 mg ESDR with HD: ceftolozane/ tazobactam 1000/500 mg immediately after HD and 2 h before HD	12	12 ceftolozane /tazo-bactam	Subjects with severe renal impairment or with ESRD requiring HD
CXA-DDI-12-10 **(2013)**	Safety, tolerability, PK, DDI furosemide, midazolam, coffeine	Phase I, single centre, open label	Single and multiple doses of ceftolozane/ tazobactam 1000/500 mg q8h for 7 days	16	16 ceftolozane /tazo-bactam	Healthy adult subjects
CXA-	Safety, efficacy,	Phase II, multicentre,	Multiple doses ceftolozane 1000 mg	127	85	Subjects with cUTI

101-03 (CUBI-RAS-002) (2009)	population PK analysis	randomised, double-blind, active comparator controlled	q8h versus ceftazidime 1000 mg q8h for 7 to 10 days		ceftolozane	(including pyelo-nephritis)
CXA-IAI-10-01 (CUBI-RAS-008) (2010)	Safety, efficacy, population PK analysis	Phase II, multicentre, randomised, double-blind, active comparator-controlled	Multiple doses ceftolozane/ tazobactam 1000/500 mg q8h +/- metronidazole 500 mg q8h versus meropenem 1000 mg q8h	121	83 ceftolozane /tazo-bactam	Subjects with cIAI

cIAI = complicated intra-abdominal infection, cUTI = Complicated urinary tract infection, DDI = drug drug interaction study, ELF = epithelial lining fluid, ESRD = end stage renal disease, HD = haemodialysis, PD = pharmacodynamics, PK = pharmacokinetics, q8h= every 8 hours, QTc = corrected QT interval

Clinical documentation to support this application includes the following pivotal and supportive studies:

Table 5: Summary of clinical studies evaluating efficacy of ceftolozane/tazobactam (cUTI indication)

Study ID	Number of Study Centres Location(s)	Study start Enrolment status, Date Total Enrolment / Enrolment goal	Design Control Type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	No. Subjects by Arm entered/ completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary and Key Secondary Endpoint
CXA-cUTI-10-04 and -05	209 centres Brazil, Bulgaria, Chile, Colombia, Croatia, Estonia, Georgia, Germany, Hungary, India, Israel, Latvia, Mexico, Moldova, Peru, Poland, Romania, Russia, Serbia, Slovakia, Slovenia, South Africa, South Korea Spain, Thailand, Ukraine, United States	28 July 2011 Completed 04 September 2013 1083/954	Phase 3, multi-centre, rand-omised, double-blind Active comp-arator/ placebo control-led	TOL/TAZ 1.5 g q8h as a 60-minute IV infusion LVX 750 mg once daily as a 60-minute IV infusion Saline Placebo as a 60-minute IV infusion	Efficacy and safety	TOL/TAZ 543/513 LVX 540/515	Treatment 7 to 9 days; TOC visit 7 (± 2) days after last dose of study drug; LFU visit 28 to 35 days after last dose of study drug	TOL/TAZ 105/293 51.0 (18, 90) LVX 103/299 49.5 (18, 87)	Clinical signs and/or symptoms of cUTI either of pyelo-nephritis or cLUTI	By-subject microbiological response rate in the ME at TOC population at the TOC visit By-subject microbiological response rate in the mMITT population at the TOC visit
CXA-101-03	20 centres 6 United States 7 Germany 7 Poland	17 August 2009 Completed 11 March 2010 129/120	Phase 2, multi-centre, rand-omised, double-blind Active comp-arator/ placebo control	TOL 1 g q8h as a 60-minute IV infusion CAZ 1 g q8h as a 60-minute IV infusion	Efficacy and safety, population PK analysis	TOL 86/81 CAZ 43/39	Treatment 7 to 10 days	TOL 43/42 62 (19-84) CAZ 26/16 70 (21-88)	cUTI including pyelo-nephritis	Per-subject microbiological response rate at the TOC visit in the mMITT and ME at TOC populations

CAZ = Ceftazidime; cLUTI = Complicated lower urinary tract infection; cUTI = Complicated urinary tract infection; F = Female; IV = Intravenous; LFU = Late follow-up; LVX = Levofloxacin; M = Male; ME = Microbiologically evaluable; mMITT = Microbiological Modified Intent-to-treat; PK = Pharmacokinetic; q8h = Every 8 hours; TOC = Test-of-Cure; TOL = Ceftolozane; TOL/TAZ = Ceftolozane/tazobactam; UTI = Urinary tract infection.

Table 6: Summary of clinical studies evaluating efficacy of ceftlozane/tazobactam (cIAI indication)

Study ID	No. of Study Centres Location(s)	Study start Enrolment status, Date Total Enrolment/ Enrolment goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. Subjects by Arm Entered/ Completed.	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary and Key Secondary Endpoints
CXA-cIAI-10-08 and -09	196 centres Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, Colombia, Croatia, Estonia, Georgia, Germany, Hungary, Israel, India, Latvia, Lithuania, Mexico, Moldova, Poland, Peru, Romania, Russia, Serbia, Slovakia, South Africa, South Korea, Spain, Ukraine, United States	Started 08 Dec 2011 Completed 15 Oct 2013 993/988	Phase 3, multicentre, double-blind, randomised Active comparator/ placebo controlled	TOL/TAZ 1.5 g q8h 60-min IV infusion plus MTZ 500 mg q8h 60-min IV infusion versus MEM 1 g q8h 60-min IV infusion plus saline placebo q8h 60-min IV infusion	Efficacy and safety	TOL/TAZ+ MTZ: 487/452 MEM: 506/476	Treatment: 4 to 14 d Subject participation: 38 to 45 d .	584/407 51 y (18, 94)	cIAI requiring surgical intervention Males or females ≥18 years of age with baseline intra-abdominal specimen for culture	Primary: Clinical cure rate in the CE population at the TOC visit Key Secondary: Clinical cure rate in the ITT population at the TOC visit
CXA-IAI-10-01	35 centres Argentina (6); Georgia (4); Russia (10); Serbia (4); United States (11)	Started 30 Jun 2010 Completed 25 Mar 2011 122/120	Phase 2, multicentre prospective, randomised, double-blind, Active comparator/ placebo controlled	TOL/TAZ 1.5 g q8h 60-min IV infusion plus MTZ 500 mg q8h 60-min IV infusion versus MEM 1 g q8h 60-min IV infusion plus saline placebo q8h 60-min IV infusion	Efficacy and safety	TOL/TAZ+ MTZ: 83/78 MEM: 39/38	Treatment: 4 to 7 d Subject participation: 26 to 36 d	69/52 47 y (18, 86)	cIAI Males or females ≥18 to 90 years of age.	Clinical cure rate at the TOC visit in the mMITT and ME populations.

CE=clinically evaluable; cIAI=complicated intra-abdominal infection; d=day(s); F=female; ITT=intent-to-treat; IV=intravenous; M=male; ME=microbiologically evaluable; MEM=meropenem; mMITT=microbiological modified intent-to-treat; MTZ=metronidazole; q8h=every 8 hours; TOC=text-of-cure; TOL/TAZ=ceftolozane/tazobactam; y=year(s).

2.4.2. Pharmacokinetics

A total of 11 phase I and II clinical studies with pharmacokinetic (PK) data are submitted, with a total of 410 subjects receiving ceftolozane, 291 subjects receiving tazobactam and 249 subjects receiving the combination of ceftolozane and tazobactam, including six studies in healthy subjects (**CXA-101-01, CXA-201-01, CXA-MD-11-07, CXA-ELF-10-03, CXA-QT-10-02, CXA-DDI-12-10**), three studies in patients with various degrees of renal impairment (**CXA-101-02, CXA-201-02, CXA-REN-11-01**), one study in patients with cUTI (**CXA-101-03**), and one study in patients with cIAI (**CXA-IAI-10-01**).

All studies used an infusion time of 60 minutes. The volumes infused were 100 mL but the concentrations of solute varied. Ceftolozane, tazobactam and tazobactam-M1 were assayed using HPLC-MS/MS methods. Laboratories used and the LLOQs varied over time but assays were appropriately validated.

In CXA-MD-11-07, CXA-REN-11-01, CXA-ELF-10-03 and CXA-DDI-12-10 and in the Phase 2 IAI (and all the Phase 3 studies) the product was supplied in vials containing 1 g ceftolozane and tazobactam sodium equivalent to 0.5 g tazobactam free acid in a lyophilised powder. The formulation used in the remaining Phase 1 studies was slightly different but no difference in PK would be expected vs. the final version.

Single dose studies

Ceftolozane doses ranged from 250-2000 mg and tazobactam doses ranged from 250-1000 mg. In study CXA-201-01 ceftolozane and tazobactam were administered separately and together to assess the effect of co-administration on PK. Ranges of observed PK parameters after single doses are shown below.

Ceftolozane (CXA-101)

Table 7

Tal Mean (CV%) PK Parameters of CXA-101 in Plasma – Part 1

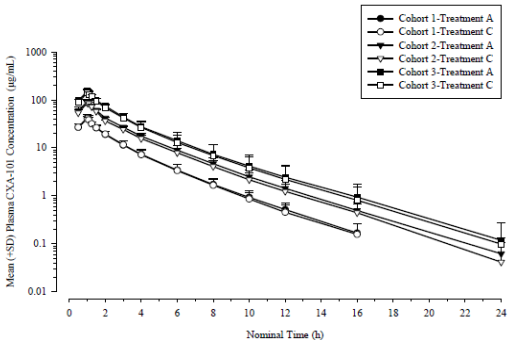
Parameter	Cohort 1		Cohort 2		Cohort 3	
	Treatment A N=6	Treatment C N=6	Treatment A N=6	Treatment C N=6	Treatment A N=6	Treatment C N=6
$AUC_{0\text{-}last}$ (µg•h/mL)	97.8 (16.4)	96.6 (14.9)	230 (5.7)	208 (8.9)	374 (16.4)	351 (18.0)
$AUC_{0\text{-}\infty}$ (µg•h/mL)	98.6 (16.3)	97.3 (15.0)	230 (5.8)	209 (9.0)	375 (16.4)	353 (18.0)
C_{max} (µg/mL)	42.6 (13.5)	40.2 (12.6)	92.3 (12.9)	90.2 (10.6)	153 (10.8)	140 (14.9)
t_{max} (h)[a]	1.00 (1.00-1.09)	1.00 (1.00-1.01)	1.01 (1.00-1.08)	1.05 (1.00-1.10)	1.01 (1.00-1.09)	1.01 (1.00-1.09)
$t_{1/2}$ (h)	2.48 (8.2)	2.43 (18.9)	2.64 (19.6)	2.58 (18.6)	2.62 (16.9)	2.62 (18.2)
CL (L/h)	5.18 (15.2)	5.23 (13.2)	4.35 (6.0)	4.82 (10.4)	5.43 (13.7)	5.81 (15.5)
V_{ss} (L)	11.8 (13.2)	11.7 (13.7)	11.0 (18.9)	11.8 (15.7)	13.3 (14.9)	14.0 (18.4)

[a]Median (min-max)
Source: Table 14.1.4.1.1 to Table 14.1.4.1.6

Cohort 1 – Treatment A = 500 mg CXA-101 Alone
Cohort 2 – Treatment A = 1000 mg CXA-101 Alone
Cohort 3 – Treatment A = 2000 mg CXA-101 Alone
Cohort 1 – Treatment C = 500 mg/250 mg CXA-101/TAZ
Cohort 2 – Treatment C = 1000 mg/500 mg CXA-101/TAZ
Cohort 3 – Treatment C = 2000 mg/1000 mg CXA-101/TAZ

Figure 3

Mean (+SD) Concentration-Time Profiles of CXA-101 in Plasma – Semi-Log Plot – Part 1



Tazobactam

Table 8

Ta[illegible]an (CV%) PK Parameters of TAZ in Plasma – Part 1

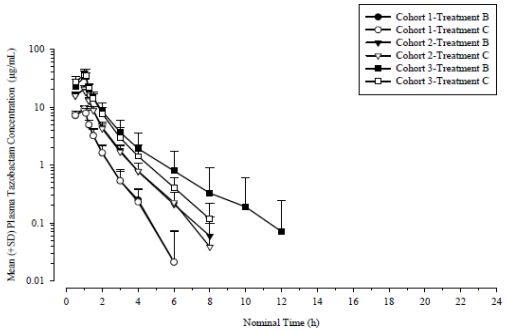
Parameter	Cohort 1		Cohort 2		Cohort 3	
	Treatment B	Treatment C	Treatment B	Treatment C	Treatment B	Treatment C
	N=6	N=6	N=6	N=6	N=6	N=6
$AUC_{0\text{-last}}$ (µg•h/mL)	11.3 (17.1)	11.5 (19.9)	28.8 (8.1)	28.6 (10.8)	50.4 (15.3)	49.8 (13.4)
$AUC_{0\text{-}\infty}$ (µg•h/mL)	11.5 (17.2)	11.7 (20.2)	29.1 (7.9)	28.8 (10.9)	50.9 (14.9)	50.1 (13.5)
C_{max} (µg/mL)	8.95 (12.4)	9.26 (15.8)	20.9 (11.3)	20.5 (13.0)	34.5 (34.8)	37.1 (13.4)
t_{max} (h)[a]	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.01 (1.00-1.01)	1.00 (1.00-1.01)	1.05 (1.00-1.25)	1.01 (1.01-1.08)
$t_{1/2}$ (h)	0.755 (20.1)	0.712 (26.6)	1.05 (25.0)	1.03 (17.7)	1.29 (47.0)	1.09 (20.2)
CL (L/h)	22.2 (17.4)	22.2 (23.0)	17.3 (8.2)	17.5 (11.4)	20.0 (13.9)	20.2 (12.6)
V_{ss} (L)	16.3 (10.6)	15.8 (17.0)	16.1 (15.4)	16.1 (17.9)	26.7 (82.3)	18.6 (16.8)

[a]Median (min-max)
Source: Table 14.1.4.4.1 to Table 14.1.4.4.6

Cohort 1 – Treatment B = 250 mg TAZ Alone
Cohort 2 – Treatment B = 500 mg TAZ Alone
Cohort 3 – Treatment B = 1000 mg TAZ Alone
Cohort 1 – Treatment C = 500 mg/250 mg CXA-101/TAZ
Cohort 2 – Treatment C = 1000 mg/500 mg CXA-101/TAZ
Cohort 3 – Treatment C = 2000 mg/1000 mg CXA-101/TAZ

Figure 4

Mean (+SD) Concentration-Time Profiles of TAZ in Plasma – Semi-Log Plot – Part 1



Tazobactam M1 metabolite

Table 9

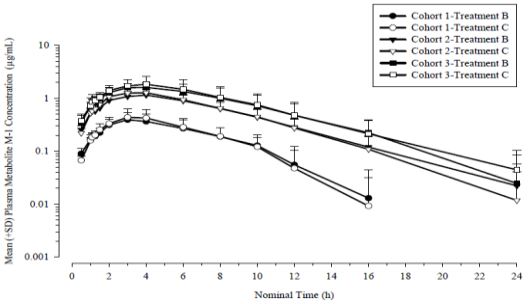
T[illegible]n (CV%) PK Parameters of Metabolite M-1 in Plasma – Part 1

Parameter	Cohort 1		Cohort 2		Cohort 3	
	Treatment B	Treatment C	Treatment B	Treatment C	Treatment B	Treatment C
	N=6	N=6	N=6	N=6	N=6	N=6
$AUC_{0\text{-last}}$ (µg•h/mL)	2.69 (45.9)	2.83 (42.9)	9.63 (33.1)	10.0 (22.4)	14.5 (42.0)	15.8 (50.2)
$AUC_{0\text{-}\infty}$ (µg•h/mL)	3.32[b] (36.5[b])	3.17 (37.4)	10.0 (32.0)	10.4 (23.1)	15.3 (40.6)	16.4 (49.5)
C_{max} (µg/mL)	0.395 (33.1)	0.444 (42.1)	1.16 (27.3)	1.34 (26.5)	1.67 (20.4)	1.89 (40.3)
t_{max} (h)[a]	3.00 (3.00-4.01)	3.00 (2.00-4.00)	4.00 (3.00-4.06)	4.01 (2.02-4.08)	3.50 (3.00-6.00)	3.50 (3.00-4.00)
$t_{1/2}$ (h)	3.30[b] (13.3[b])	3.20 (32.8)	3.48 (23.7)	3.05 (29.0)	3.42 (14.3)	3.77 (27.5)
CL/F_m (L/h)	68.2[b] (29.9[b])	72.1 (31.7)	44.6 (28.5)	41.5 (23.9)	59.7 (29.1)	57.6 (30.9)
V_{ss}/F_m (L)	404[b] (26.1[b])	428 (42.5)	286 (26.9)	248 (22.7)	381 (20.6)	378 (30.5)

[a]Median (min-max)
[b]N=5. The concentration-time profile for Subject 1102 did not exhibit a terminal log-linear phase. The PK parameters $AUC_{0\text{-}\infty}$, $t_{1/2}$, λ_z and CL/F_m and V_{ss}/F_m could not be calculated.

Figure 5

Mean (+SD) Concentration-Time Profiles of metabolite M-1 in Plasma – Semi-Log Plot – Part 1



Multiple dose studies

In CXA-201-01 1 g/0.5 g and 2 g/1g ceftolozane/tazobactam was administered q8h for 10 days. There was no accumulation observed for either substance.

Tables 10 & 11

nmary of Plasma Pharmacokinetic Parameters of CXA-101 Following the Administration of Single ...l Multiple Doses of CXA-201 (Median and Range)

	1.5 gram Dose (1 gram CXA-101)			3 gram Dose (2 grams CXA-101)		
Parameter	**Day 1**	**Day 5**	**Day 10**	**Day 1**	**Day 5**	**Day 10**
$t_{1/2}$ (hr)	1.93 (1.81 - 2.12)	1.98 (1.68 - 2.25)	2.13 (2.11 - 2.72)	2.0 (1.8 - 2.3)	2.1 (1.8 - 2.3)	2.7 (2.4 - 3.6)
C_{max} (µg/mL)	44.2 (38.9 - 58.8)	57.5 (55.0 - 75.2)	59.6 (53.5 - 63.4)	109.0 (80.0 - 116.0)	122.0 (109.0 - 149.0)	117.0 (85.0 - 128.0)
T_{max} (hr)	1.0 (0.5 - 1.0)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)
C_{last} (µg/mL)	2.9 (2.3 - 3.6)	3.2 (2.9 - 3.7)	0.6 (0.3 - 0.9)	7.1 (5.3 - 11.1)	6.7 (5.3 - 9.6)	0.6 (0.3 - 1.1)
T_{last} (hr)	8.0 (8.0 - 8.0)	8.0 (8.0 - 8.0)	14.0 (12.0 - 16.0)	8.0 (8.0 - 8.0)	8.0 (8.0 - 8.0)	16.0 (16.0 – 24.0)
$AUC_{0-\tau}$ (µg*hr/mL)	122.0 (111.4 - 158.9)	107.6 (103.2 - 134.5)	143.7 (130.4 - 161.5)	277.3 (236.6 - 304.5)	315.5 (274.9 - 358.0)	300.8 (245.1 - 342.8)
$AUC_{0-\infty}$ (µg*hr/mL)	130.1 (117.5 - 169.8)	110.6 (105.7 - 137.0)	ND	298.4 (251.0 - 340.6)	ND	ND
Clearance (L/hr)	8.2 (6.3 - 9.0)	9.1 (7.3 - 9.5)	7.0 (6.2 - 7.7)	7.2 (6.6 - 8.5)	6.3 (5.6 - 7.3)	6.7 (5.8 - 8.2)
V_{ss} (L)	20.9 (15.5 - 21.7)	19.3 (13.0 - 21.1)	17.1 (15.2 – 19.0)	19.4 (18.6 - 22.3)	15.4 (14.9 - 17.8)	17.6 (15.9 - 21.4)
Accumulation Index	ND	ND	1.1 (1.1 - 1.2)	ND	ND	1.1 (1.1 - 1.3)

T: nmary of Plasma Pharmacokinetic Parameters of Tazobactam Following the Administration of Single ...l Multiple Doses of CXA-201 (Median and Range)

	1.5 gram Dose (0.5 grams tazobactam)			3 gram Dose (1 gram tazobactam)		
Parameter	**Day 1**	**Day 5**	**Day 10**	**Day 1**	**Day 5**	**Day 10**
$t_{1/2}$ (hr)	0.91 (0.87 - 1.01)	0.8 (0.8 - 0.9)	0.9 (0.9 - 0.9)	1.02 (0.75 - 1.15)	1.0 (0.8 - 1.4)	1.0 (0.8 - 1.3)
C_{max} (µg/mL)	12.2 (10.7 - 14.0)	14.0 (12.5 - 19.6)	13.1 (12.4 - 18.0)	28.5 (22.7 - 31.5)	30.6 (25.1 - 36.3)	26.5 (20.1 - 32.1)
T_{max} (hr)	0.8 (0.5 - 1.0)	1.0 (1.0 - 1.0)	1.0 (1.0 - 1.0)	1.0 (0.5 - 1.0)	1.00 (1.00 - 1.00)	1.0 (0.5 - 1.0)
C_{last} (µg/mL)	0.2 (0.2 - 0.5)	0.1 (0.1 - 0.4)	0.4 (0.1 - 0.5)	0.2 (0.2 - 0.3)	0.2 (0.1 - 0.3)	0.2 (0.1 - 0.3)
T_{last} (hr)	6.0 (4.0 - 6.0)	6.0 (4.0 - 6.0)	4.0 (4.0 - 6.0)	8.0 (6.0 - 8.0)	8.0 (6.0 - 8.0)	8.0 (6.0 - 8.0)
$AUC_{0-\tau}$ (µg*hr/mL)	19.6 (18.5 - 22.8)	19.3 (19.0 - 19.7)	23.2 (23.2 - 23.2)	47.9 (40.8 - 53.3)	45.6 (36.0 - 58.9)	39.6 (34.8 - 50.9)
$AUC_{0-\infty}$ (µg*hr/mL)	19.7 (18.6 - 22.8)	ND	ND	48.1 (41.1 - 53.7)	ND	ND
Clearance (L/hr)	25.5 (21.9 - 27.0)	26.0 (25.4 - 26.3)	21.6 (21.6 - 21.6)	20.9 (18.8 - 24.5)	21.9 (17.0 - 27.8)	25.3 (19.7 - 28.8)
V_{ss} (L)	26.8 (21.6 - 27.3)	22.7 (21.9 - 23.1)	18.4 (18.4 - 18.4)	23.8 (20.4 - 27.0)	24.1 (18.4 - 26.8)	24.4 (21.1 - 30.0)
Accumulation Index	ND	ND	1.0 (1.0 - 1.0)	ND	ND	1.0 (1.0 - 1.0)

There was an apparent dose-proportional increase in exposure with no substantial differences in clearance and volume of distribution for both actives after single and multiple doses.

Co-administration of CXA and TAZ did not affect the PK of each other. The time courses of plasma concentrations for each of ceftolozane and tazobactam as well as the M-1 metabolite of tazobactam were similar to those when equivalent doses were given alone

Distribution & metabolism

- In-vitro studies indicated that human plasma protein binding of ceftolozane is low (~16 to 21%). The reported binding for tazobactam is approximately 30%.
- Ceftolozane exhibited low partitioning to blood cells.
- The volume of distribution for ceftolozane ranged between ~12 and 17 L in multiple dose studies in healthy volunteers and was similar to that for tazobactam (~14 to 18L).
- In the final POPPK model Vc in healthy subjects and patients was from 11-18 L. For tazobactam, Vc in healthy subjects was approximately 14 L but was about 47% greater in Phase 2 IAI patients.

CXA-ELF-10-03 investigated ELF penetration after 1 g/500 mg ceftolozane-tazobactam q8h and reported respective penetration ratios of 48% and 54%. The ELF concentrations of ceftolozane exceeded 8µg/mL for approximately 60% of the dosing interval.

A mass balance study was not conducted. Human PK data suggested that ceftolozane does not undergo significant metabolism *in vivo.*

Tazobactam is partially converted to the ring-open inactive M-1 metabolite. Steady state for M-1 appears to be reached by day 4 and some modest accumulation occurs in plasma. Exposure to the M-1 metabolite increased in an apparent dose-proportional manner and was generally <10% of that of tazobactam.

Elimination

The vast majority of ceftolozane was excreted in the urine in humans as unchanged parent drug. Renal CL of ceftolozane was highly correlated to CrCL and was similar to CL indicating that the systemic elimination of ceftolozane is primarily renal. Renal CL was similar GFR for the unbound fraction indicating that tubular secretion does not contribute to renal excretion of ceftolozane. In contrast, CLr of tazobactam exceeds GFR for the unbound fraction, indicating that tubular secretion contributes to the renal excretion of tazobactam.

The elimination half-lives of each of ceftolozane and tazobactam were not affected by dose or duration of dosing when given alone or in combination. The plasma CL and CLr for each of ceftolozane and tazobactam increased with increasing CrCL regardless of co-administration.

Intra- and inter-individual variability

In CXA-QT-10-02 intra-subject variability was <10% for ceftolozane and ~12% for tazobactam. In healthy subjects with normal CrCL inter-subject variability (CV%) was low for ceftolozane (generally < 20% for AUC and Cmax) and tazobactam (< 25% for AUC and Cmax). Inter-subject variability for ceftolozane in patients with cUTI was similar to that in healthy subjects (CV% 18% for Cmax and 26% for AUC) but variability for both actives was higher in patients with cIAI, in particular for tazobactam.

Time dependency

Ceftolozane and tazobactam do not exhibit time-dependent PK. The inactive M-1 metabolite does show some accumulation in plasma during multiple dosing.

Special populations

Renal impairment

- In subjects with mild renal impairment (estimated CrCL ≥50 to ≤80 mL/min) the ceftolozane mean Cmax, AUC0-last and AUC0-∞ were 1.2- and 1.3-fold increased vs. controls and mean t1/2 values were similar at 3.2 h. Subjects with moderate impairment (estimated CrCL ≥30 to <50 mL/min) had ~2.5-fold higher plasma exposures and the t1/2 was ~2-fold longer.

- In subjects with mild impairment the tazobactam mean Cmax, AUC0-last and AUC0-∞ were up to 37% higher than for controls but mean t1/2 values were similar. In subjects with moderate renal impairment mean AUC0-last and AUC0-∞ were 2-fold higher and the mean t1/2 was 1.6-fold longer. Mean plasma CL decreased 2-fold and was 1.7-fold lower after normalisation by weight while mean CLr was 2-fold lower and mean urine recovery was slightly reduced (64% vs. 75%).
- There was little difference in the PK of metabolite M-1 in those with mild renal impairment vs. controls but those with moderate impairment had increased exposures associated with the decrease in tazobactam CL so that the AUCm/AUCp ratio was 2.6-fold higher vs. the control group.

In subjects with severe renal impairment (CrCL < 30 mL/min) plasma concentrations of ceftolozane declined with a median t1/2 of 11.1 h and were quantifiable for > 48 h. Tazobactam declined with a median half-life of 2.5 h and was quantifiable in plasma for up to 12 h. CLr for both drugs was reduced.

An analysis of PK data obtained from the start of the infusion to the end of dialysis to determine the contribution of HD to removal of the 3 analytes showed that concentrations of each analyte declined rapidly following the start of dialysis with median t1/2 values < 2 h. More than 90% of the administered dose was removed by dialysis with concentrations just before the end of dialysis (C_{last}) that were 14-, 32- and 26-fold lower than the respective Cmax values.

The POPPK analysis (CUBI-PCS-100) resulted in the following conclusions:

- There was no clinically meaningful difference in AUCss (<27% difference) between normal renal function and mild impairment in the absence of infection, suggesting no dose adjustment is needed.
- The GM dose-normalised Cmaxss and AUCss in moderate renal impairment without infection were about 2 to 3-fold those in normal renal function. This suggested a 2-fold dose reduction to 500 mg/250 mg in moderate renal impairment.
- The GM dose-normalised Cmaxss and AUCss in severe renal impairment in the absence of infection were about 3 to 6-fold those in normal renal function. This suggested a 4-fold dose reduction to 250 mg/125 mg in severe renal impairment.

Hepatic impairment

No clinical studies were conducted to assess the effect of hepatic impairment on the PK of ceftolozane. Ceftolozane does not appear to undergo hepatic metabolism or biliary excretion, and changes in PK are not expected in hepatic impairment. Tazobactam t½ increases by 18% in subjects with hepatic cirrhosis compared to that in healthy subjects and no dose adjustment is recommended in these patients.

Elderly

In the population PK analysis **CUBI-PCS-100**, 376 subjects of 18 to 86 years of age were included in the population PK analysis of ceftolozane and 249 subjects of 18 to 86 years of age were included in the population PK analysis of ceftolozane of tazobactam, or ceftolozane/tazobactam. A small negative trend was observed between age and the clearance variability for both ceftolozane and tazobactam. However age were not identified alone to significantly influence the PK of ceftolozane/tazobactam.

A breakdown of numbers of subjects/patients aged 65-74 years, 75-84 years and ≥ 85 years enrolled into PK, Phase 2 and Phase 3 studies is shown below. A few subjects had no PK information due to withdrawal from study or incomplete sampling. PK sampling was not performed in the Phase 3 cUTI and cIAI studies.

Table 12

Tal Number of Elderly Patients Enrolled in the Ceftolozane/Tazobactam Development Program

Age Category (years)	Phase 1 (PK) Studies		Phase 2 Studies		Phase 3 Studies		Total	
	Total subjects	Subjects with PK data	Total subjects	Subjects with PK data	Total subjects	Subjects with PK data	Total subjects	Subjects with PK data
65-74	16	16	32	30	137	0	185	46
75-84	6	6	24	22	101	0	131	28
≥85	0	0	2	2	12	0	14	2
Total	22	22	58	54	250	0	330	76

Children

No studies were conducted to examine the PK of ceftolozane/tazobactam in children.

Pharmacokinetics in target population

The final POPPK analysis included data from 8 phase 1 studies in healthy subjects and subjects with renal impairment as well as data from the patients enrolled in Phase 2 studies in IAI and UTI.

A total of 376 (212 males/164 females) subjects with 5048 measurable ceftolozane PK samples and 243 (139 males/104 females) subjects with 2683 measurable tazobactam PK samples were included in the PPK analysis. Overall, 40% and 32% of subjects with ceftolozane and tazobactam measurable PK samples, respectively, were subjects with infection. Among the 73 subjects with UTI, 21 had pyelonephritis. Among the 77 subjects with IAI, 32 had appendicitis.

The final PK model for ceftolozane was a 2-compartment disposition model with linear elimination including the effect of baseline CrCL on CL and body weight on Vc, and the effect of UTI and IAI infection on both CL and Vc. While body weight was statistically significant covariate for ceftolozane volume of distribution it did not influence exposure alone in a clinically meaningful manner. Ceftolozane CL is predicted to change by about 15% for a change of every 20% in CrCL and by about 20% in subjects with UTI or IAI. The Vc would change by about 20% for a change of every 20% in body weight, except in subjects with cIAI. In the final model for ceftolozane the presence or absence of bacterial infection was an important component explaining the variability of CL and Vc. For a typical subject without any infection the estimate of t½β for ceftolozane was 3.07 h and for a population with bacterial infections the estimate of t½β was 3.00 h.

The final PK model for tazobactam was a 2-compartment disposition model with linear elimination, including the effect of baseline CrCL on CL and IAI infection on Vc. CL is predicted to change by about 14% for a change of every 20% in CrCL. The Vc is about 47% larger in patients with IAI as compared to healthy subjects.

Table 13

Ta **ımary of Dose-Normalised Ceftolozane Pharmacokinetic Exposure Parameters at Steady-State by Infection Status in Subjects with Creatinine Clearance ≥90 mL/min (Report CUBI-PCS-100)**

Infection	Mean (CV%) Geometric mean [Minimum- Maximum]					
	$C_{min,ss}$/Dose (µg/mL/mg)	$C_{max,ss}$/Dose (µg/mL/mg)	$AUC_{\tau,ss}$/Dose ([µg•h/mL]/mg)	V_c (L)	CL (L/h)	$t_{½\beta}$ (h)
Yes, cUTI (n=21)	0.00519 (91.0) 0.00405 [0.00144-0.0198]	0.0567 (24.0) 0.0553 [0.0373-0.0970]	0.163 (26.1) 0.158 [0.0962-0.287]	16.4 (38.1) 15.5 [7.42-37.2]	6.51 (24.4) 6.32 [3.49-10.4]	2.81 (35.0) 2.71 [2.15-6.19]
Yes, cIAI (n=48)	0.00810 (314.3) 0.00305 [0.000868-0.175]	0.0557 (93.0) 0.0459 [0.0247-0.252]	0.169 (137.9) 0.130 [0.0656-1.61]	21.6 (44.5) 18.6 [0.878-53.4]	8.54 (34.4) 7.71 [0.620-15.2]	3.16 (90.8) 2.72 [2.03-19.36]
No, HVs (n=186)	0.00307 (73.7) 0.00242 [0.000452-0.0192]	0.0699 (28.7) 0.0680 [0.0429-0.258]	0.177 (25.4) 0.173 [0.111-0.590]	11.8 (24.9) 11.4 [2.53-21.4]	5.89 (18.2) 5.78 [1.69-9.02]	2.49 (8.3) 2.48 [2.16-3.65]

$AUC_{\tau,ss}$/dose=Area under the curve from time 0 to 8 hours post-dose at steady-state for a 1000-mg dose computed as dose/CL; cIAI=complicated intra-abdominal infection; CL=total body clearance from the plasma; $C_{max,ss}$=maximum concentration at steady state achieved at the end of a 1-hour infusion; $C_{min,ss}$=minimum concentration at steady state; cUTI=complicated urinary tract infection; CV=coefficient of variation; HV=healthy volunteer; IV=intravenous; $t_{½\beta}$=elimination half-life; V_c=apparent central volume of distribution after IV administration

Source: M5.3.3.5\CUBI-PCS-100\Table 13

Body weight was identified to be significant in Vc for the patients with cUTI but it did not impact drug clearance. Body weight might indirectly impact AUC through renal clearance which is a function of body weight but renal function is used to adjust the dose of ceftolozane/tazobactam.

Therefore, there is no recommendation for dose adjustment based on body weight alone. This position was further supported by Monte Carlo simulations where >90% target attainment for ceftolozane was achieved in severely/morbidly obese patients (BMI ≥ 35) following the proposed dose adjustment based on renal function (based on the target of 1-log kill at 32.2% *f*T>MIC).

None of other examined covariates (e.g. age, sex and race), were identified alone to significantly influence the PK of ceftolozane or tazobactam.

While infection was an important covariate explaining the variability in CL and Vc for ceftolozane and Vc for tazobactam, its effect on PK was not considered clinically meaningful as any exposure changes were limited to less than 20%.

Pharmacokinetic interaction studies

In vitro

- Ceftolozane did not demonstrate relevant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 (IC50 >300 µM) indicating low potential to cause clinically relevant inhibition of these CYP isoforms. Ceftolozane demonstrated no potential to cause time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at concentrations up to and including 6000 µg/mL.
- Ceftolozane showed no potential to induce CYP1A2, CYP2B6 or CYP3A4 up to and including 1000 µg/mL (nominal concentration), the highest concentration assessed in cultured cryopreserved human hepatocytes.
- Ceftolozane is not a substrate for P-gp and BCRP. It showed no potential inhibitory interaction against OAT1, OAT3, OCT1, OCT2, OATP1B1 or OATP1B3 transporters at concentrations up to 500 µg/mL. In a separate study there was no inhibition of P-gp, BCRP, BSEP or MRP2 at concentrations up to 2500 µg/mL. Ceftolozane demonstrated dose-dependent inhibition of both MATE1 and MATE2-K transporters up to a concentration of 2500 µg/mL but there is a low potential for clinically relevant inhibition to occur.
- Tazobactam demonstrated no relevant potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6. Tazobactam did not induce CYP1A2, CYP2B6 or CYP3A4 based on catalytic activity and mRNA expression assays at up to 500 µg/mL. There was also no induction of CYP1A2, CYP2B6 or CYP3A4 at concentrations up to and including 1250 µg/mL.
- Tazobactam is a substrate for the OAT1 and OAT3 transporters, consistent with its known interaction with probenecid. It is not a substrate for P-gp, BCRP or OCT2 human transporters. Tazobactam demonstrated no potential to inhibit P-gp, BCRP or BSEP at up to 900 µg/mL (~58-

fold unbound Cmax). Tazobactam inhibited OAT1 and OAT3 transporters with IC50 values of approximately 118 and 147 µg/mL, respectively.

- The M-1 metabolite did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at 150 µg/mL. There was no induction of CYP1A2, CYP2B6 or CYP3A4 at 75 µg/mL but there was a concentration-dependent decrease in mRNA levels and enzyme activity across all donors for all three isoforms tested.
- There was no inhibition of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, BSEP, BCRP or MDR1 transporter function at 75 µg/mL. Inhibition of OAT1 occurred with an estimated IC50 >75 µg/mL, corresponding to ~50-fold mean Cmax and a low potential for clinically relevant inhibition.

In vivo
A clinical DDI study evaluated the ceftolozane/tazobactam drug interaction potential using CYP1A2, CYP3A4 and OAT1/OAT3 probe substrate drugs (caffeine, midazolam and furosemide, respectively). For the OAT1 and OAT3 substrate furosemide the decreases in AUC_{0-t} and Cmax were ~12% and 17%, respectively.

For the CYP1A2 substrate caffeine there was no appreciable effect of co-administration. For the caffeine metabolite 1,7-dimethylxanthine there was a 1.15-fold increase in mean $AUC_{0-\infty}$ and an increase in AUC_{0-t} (29%) on co-administration. Both GMRs and 90% CIs exceeded 1.25. For the CYP3A4 substrate midazolam the mean Cmax was increased 1.15-fold and $AUC_{0-\infty}$ was increased 1.23. The 90% CI around the GMRs on Day 12 fell within 80, 125% but slightly exceeded 125% on Day 15.

The applicant concluded that there was minimal potential for clinically relevant drug interactions as all GMRs were < 1.25 except for 1,7-dimethylxanthine.

2.4.3. Pharmacodynamics

Mechanism of action
The primary mechanism of action of ceftolozane is the same as for all other beta-lactam agents, i.e. inhibition of the transpeptidation step of bacterial peptidoglycan biosynthesis by inactivation of PBPs. The spectrum of activity of ceftolozane includes enterobacteria, non-fermenters, fastidious Gram-negative organisms, some streptococci and a few selected anaerobes. Ceftolozane alone is stable in the presence of those beta-lactamases that generally do not hydrolyse cephalosporins (such as TEM-1) but it is readily hydrolysed by a wide range of ESBLs and by AmpC enzymes produced by some genera, such as *Enterobacter spp*. However, it is relatively stable in the presence of pseudomonal AmpC enzymes, is not affected by loss of OprD and is a poor substrate for pseudomonal efflux pumps, making it a potentially useful agent for some MDR *P. aeruginosa*.

Tazobactam has no useful direct antibacterial activity. It inhibits a range of chromosomal- and plasmid-mediated bacterial class A and class C β-lactamases. Tazobactam does not or does not reliably inhibit many beta-lactamases that are now emerging especially in association with MDR and PDR phenotypes, including (but not limited to) the enterobacterial plasmid-borne AmpC enzymes (CMY and FOX), KPC-2/3, OXA-types, PSE-like and VEB-5 enzymes or any metallo-enzymes. For susceptibility testing of the combination, MICs of ceftolozane were determined using broth microdilution in the presence of a fixed 4 µg/mL concentration of tazobactam, which was supposedly chosen to distinguish the enzymes that can and cannot be inhibited by tazobactam.

Primary and Secondary pharmacology
Microbiology

Large scale surveillance studies of ceftolozane and ceftolozane/tazobactam susceptibility were performed in N. America and the EU and included more than 33,000 contemporary (2008-2012) strains.

- More than 99% of E. coli strains were inhibited by 8 µg/mL with MIC50/90 at 0.25/0.5 µg/mL overall and 0.5/4 µg/ml for strains with an ESBL phenotype. For non-ESBL-producing E. coli the highest MIC observed was 2 µg/ml.
- For K. pneumoniae with an ESBL phenotype the MIC90 was >32 µg/mL vs. 0.5 µg/ml for non-ESBL strains.
- For Enterobacter spp. the MIC90 was 0.5 µg/mL for ceftazidime-susceptible strains vs. 32 µg/mL for ceftazidime non-susceptible strains.
- The MIC90 was ≤1 µg/mL for Citrobacter koseri, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri, Salmonella spp., Serratia liquefaciens and Serratia marcescens. Upward shifts were observed for ESBL producers (e.g. for P. mirabilis MIC90 was 16 µg/mL).
- The MIC90 for Acinetobacter spp. and S. maltophilia was > 32 µg/mL while MIC90 values observed for H. influenzae, S. pneumoniae and beta- haemolytic streptococci were 0.12, 4 and 0.5 µg/mL, respectively, based < 100 isolates of each.
- For P. aeruginosa in the EU a substantial proportion had MICs ≥16 µg/mL, mostly due to the presence of metallo-enzymes in Eastern European isolates. However, some produced serine-based enzymes that can hydrolyse ceftolozane and are not inhibited by tazobactam.

Pharmacodynamic models

In a mouse sepsis model, ceftolozane/tazobactam in a ratio of 2:1 was effective against ESBL-positive *E. coli* and *K. pneumoniae* and ceftolozane alone was effective against wild-type *Enterobacteriaceae, S. pneumoniae* and MDR *P. aeruginosa*. Of interest, while the MIC for ESBL positive and negative *E coli* was the same (0.25 µg/mL) the ceftolozane ED_{50} increased from 0.3 to 25.9 mg/kg.

In further studies ceftolozane and ceftolozane/tazobactam were effective in systemic infection models including sepsis, pneumonia, UTI and infected burns in mice caused by *P. aeruginosa* (including MDR strains) and *Enterobacteriaceae* (including ESBL-producing strains). These studies identified the following targets for **ceftolozane**, noting that MICs did not *per se* affect the targets. It should also be noted that targets are for total and not free drug. However, protein binding estimates were taken into account in the Monte Carlo simulations use to estimate the probability of Target attainment (PTA).

Table 14

Ta **rcent T>MIC Required for Bacteriostasis and Bactericidal Activity ainst Enterobacteriaceae and *Pseudomonas aeruginosa***

Organism	Ceftolozane MIC (µg/mL)	Percent (%) T > MIC of Ceftolozane		
		Bacteriostasis	1-$\log_{10}$ kill	2-$\log_{10}$ kill
Enterobacteriaceae				
E. coli ATCC 25922	0.5	28.1	32.8	42.2
E. coli NIH-J	0.06	28.0	32.3	40.8
K. pneumoniae ATCC 43816	1 – 2	25.2	32.0	43.4
K. pneumoniae 216	1	24.0	29.2	40.9
Mean ±SD		**26.3 ± 2.1**	**31.6 ± 1.6**	**41.8 ± 1.2**
P. aeruginosa				
ATCC 27853	0.5	24.3	33.9	66.0
4034A	0.5 -1	28.5	35.3	45.7
PO2	0.5	21.7	30.1	61.6
313	1	21.4	26.7	35.5
Mean ±SD		**24.0 ± 3.3**	**31.5 ± 3.9**	**52.2 ± 14.1**
Overall Median for all strains		**24.8**	**32.2**	**42.8**

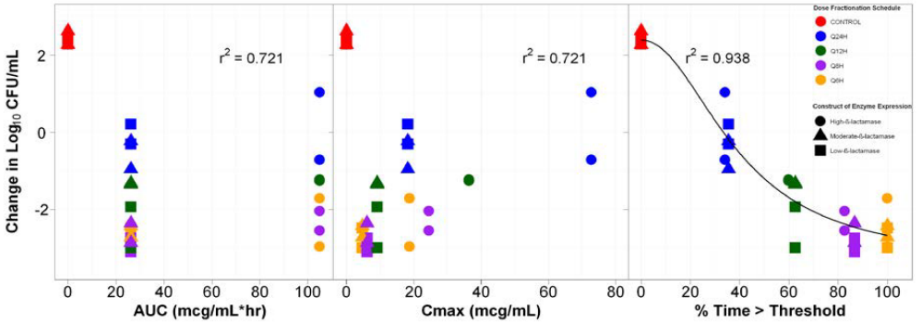
%T>MIC=time as a percentage of the dosing interval the drug concentrations exceeds the MIC;

For **tazobactam** %T>threshold was identified as the PK/PD parameter of importance. For example, analysis of the exposure-response in the mouse neutropenic thigh infection model and using *E. coli* and *K. pneumoniae* showed that a tazobactam threshold of 1 µg/mL correlated best with efficacy.

In-vitro dose fractionation studies using *E. coli* producing different amounts of CTX-M-15 also clearly demonstrated the relationship between %T>threshold for tazobactam (see below). The tazobactam threshold was 0.05 µg/mL for strains with low or moderate expression of CTX-M-15 and 0.25 µg/mL for high expression. The time necessary for bacterial stasis at 24 h was 35% of the dosing interval regardless of enzyme production.

Figure 6

Fig **elationships Between 3 Tazobactam Exposure Measures AUC, C_{max}, and %T>Threshold and Change in $\log_{10}$ CFU in Isogenic CTX-M-15 Producing *E. coli* After 24 Hours of Therapy in a PK/PD In Vitro Infection Model**

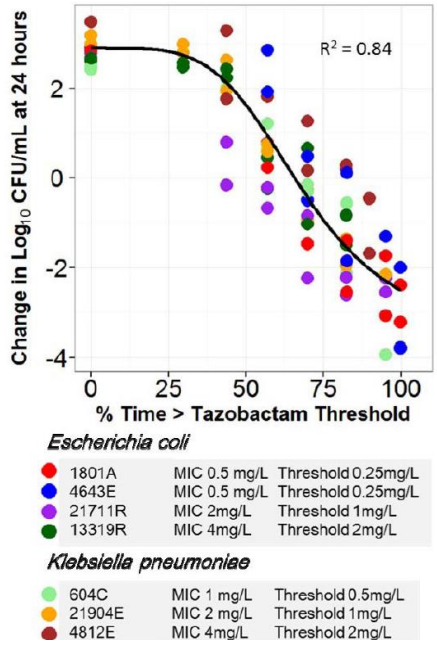


Further studies with different species and enzymes in the same model indicated that thresholds varied from 0.5 to 4 µg/mL tazobactam.

However, when the individual isolate ceftolozane MIC (with tazobactam 4 µg/mL) was transformed by a factor of 0.5, a unifying relationship for each bacterial genus was identified. This translational relationship allowed for the co-modelling of exposure-response ceftolozane/tazobactam relationships across isolates. The %T> threshold required for stasis, log 1 and 2 reduction was estimated at 65%, 77% and 90% (these estimates were applicable to *E. coli* and *K. pneumoniae* with MICs up to 4 µg/mL).

Figure 7

Fi e Relationship Between Tazobactam %T>Threshold and Change in Log_{10} CFU From Baseline at 24 Hours for *Escherichia coli* and *Klebsiella pneumoniae* in a PK/PD In Vitro Infection Model



Data from this empirical relationship analysis are shown in the next table. The calculated tazobactam %T>threshold for stasis was similar for the clinical strains but higher than for the isogenic strains. The applicant states that this may reflect the presence of multiple β-lactamases and additional resistance determinants in the clinical isolates. It is also stated that the relevance of this empirical relationship should be studied using clinical outcome data with adequate sample size for higher MIC values.

Table 15

T nmary of Tazobactam %T> Threshold for Isogenic *Escherichia coli* ains and Genetically Characterised Clinical *Escherichia coli* and *Klebsiella pneumoniae* Strains

Organism	N	MIC (µg/mL)	Tazobactam Threshold[c]	R^2	%T>Threshold (Stasis)
Escherichia coli isogenic[a]	3	0.25	0.05 – 0.25	0.94	35.0
Escherichia coli clinical[b]	4	0.5 – 4	0.5 – 2.0	0.90	65.7
Klebsiella pneumoniae clinical[b]	3	1 - 4	0.5 – 2.0	0.76	65.8
All clinical strains	7	0.5 - 4	0.25 – 2.0	0.84	65.9

%T=time as percentage of the dosing interval that the drug concentration remains above the threshold; MIC=minimum inhibitory concentration; R^2=correlation coefficient. Stasis was used as the target for tazobactam as tazobactam is a β-lactamase inhibitor and has no inherent bactericidal activity.

Relationship between concentration and effect

The proposed ceftolozane/tazobactam dose regimen for cUTI and IAI is 1g/0.5 g q8h using 1-h infusions. This regimen was selected based on PTA analyses using the targets described above and using Monte-Carlo simulations (MCS).

MCS were conducted to determine PTA based on **ceftolozane** f%T>MIC targets for *P. aeruginosa.* PK profiles were simulated for 5,000 patients, with 1,000 in each of 5 renal function categories and adjusted doses, all using 1-h infusions, as follows:

- High normal renal function (150 < to 200 mL/min): 1000/500 mg q8h
- Normal renal function (90 to < 150 mL/min): 1000/500 mg q8h
- Mild renal impairment (50 to < 90 mL/min): 1000/500 mg q8h
- Moderate renal impairment (29 to 50 mL/min): 500/250 mg q8h
- Severe renal impairment (15 to < 29 mL/min): 250/125 mg q8h

Table 16

T robability of Target Attainment for Ceftolozane/Tazobactam Dosing Regimens by MIC and Renal Function Category

Renal Function Category	Ceftolozane/Tazobactam Dosing Regimen (mg)	MIC (mg/L)	Percent (%) of Simulated Subjects Achieving Free-drug %T>MIC Targets ≥24.8/≥32.2[a]
High normal	1000/500	4	99.5/96.1
Normal	1000/500	8	99.1/94.7
Mild	1000/500	8	100/99.8
Moderate	500/250	8	99.9/99.5
Severe	250/125	8	98.4/96.1

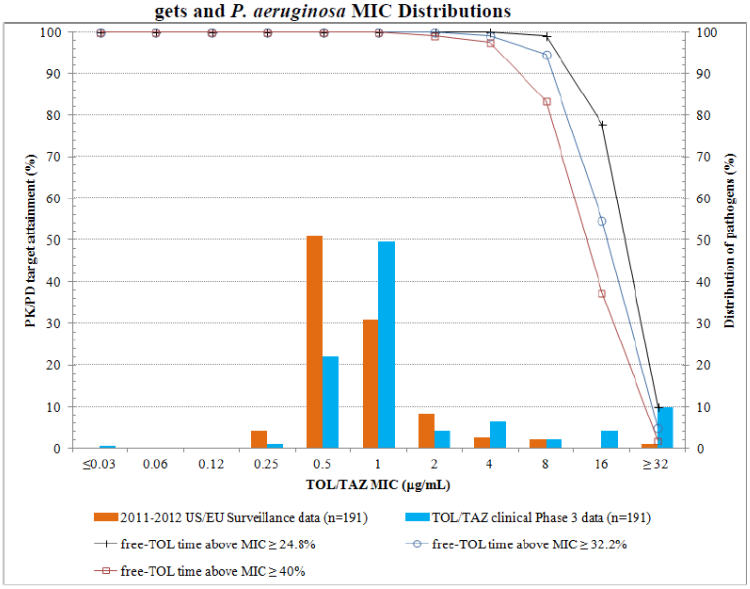
%T>MIC=time as percentage of dosing interval the drug concentration exceeds the MIC; MIC=minimum inhibitory concentration; PTA=probability of target attainment

[a] Represents an MIC value associated with ≥90% PTA.

The figure shows the results of simulations for those with normal renal function. At the 1-log kill target (blue line) the 1 g q8h ceftolozane dose is supported for strains with MICs up to 8 µg/mL.

Figure 8

Fi centage of Simulated Subjects Achieving Free-Drug % T>MIC gets and *P. aeruginosa* MIC Distributions



The PTA for *Streptococcus spp.* and for *Enterobacteriaceae* was assessed separately but in a similar fashion. The table shows PTA taking into account MIC ranges reported for 2011 surveillance and Phase 3 clinical isolates.

Table 17

T mulated Cumulative Fraction of Response for Ceftolozane/tazobactam Against Key Clinical and Surveillance Pathogens

	Percent CFR					
	24.8% *f*T>MIC		32.2% *f*T>MIC		40% *f*T>MIC	
Pathogens	Surveillance	Phase 3	Surveillance	Phase 3	Surveillance	Phase 3
Enterobacteriaceae	98.1	97.5	97.8	97.0	97.5	96.6
P. aeruginosa	99.0	90.1	98.9	88.5	98.5	87.1
S. anginosus, S. constellatus, and *S. salivarius*	100.0	98.1	99.9	96.2	99.6	92.8

%*f*T>MIC=Time as percentage of the dosing interval that the free drug concentration exceeds the MIC; CFR= cumulative fraction of response; MIC=minimum inhibitory concentration

Additional simulations were conducted to justify the ceftolozane dose regimens by examining the exposure and the PTA at the proposed doses across the full renal clearance range after incorporating the observed variability including both the covariate effects and the random effects that were identified in the POPPK model. The results were reported separately for cIAI vs. cUTI, considering the variability in PK between the two indications.

Overall, at the proposed dose for each renal function category, the achievable PTA was slightly different between indications but it was ~90% or greater for bactericidal activity (1-log kill with 32.2% *f*T>MIC) at a ceftolozane MIC of 8 mg/L in patients at the upper end of each renal function category (e.g. CrCL=29, 50 or 150 mL/min).

For patients with hyper renal clearance (CrCL>150 to 250 mL/min) simulation suggested >90% PTA for the 1-log kill target for ceftolozane MICs up to 4 mg/L for both cIAI and cUTI and a range of 70% (cUTI)

-90% (cIAI) for MICs up to 8 mg/L using 1 g/0.5 g q8h and 1-h infusions.

Figures 9 & 10

Figu lated Target Attainment in Plasma in Patients with cIAI at CLcr=250 mL/min Following Administration of 1 g/0.5 g Ceftolozane/Tazobactam, 1-hr Infusion, Every 8 hours

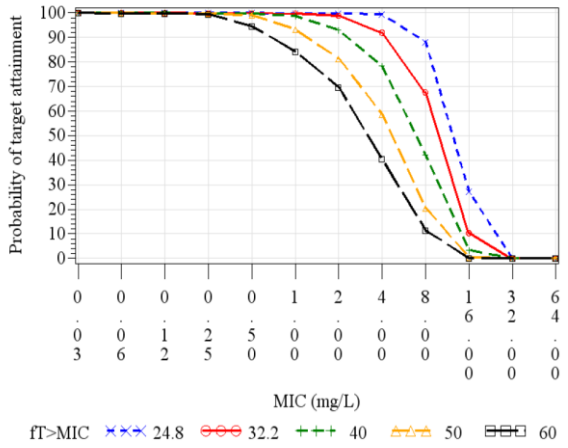
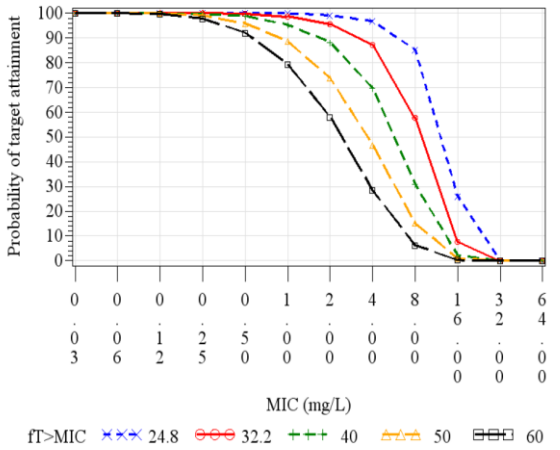


Fig lated Target Attainment in Plasma in Patients with cUTI at CLcr=250 ...min Following Administration of 1 g/0.5 g Ceftolozane/Tazobactam, 1-hr Infusion, Every 8 hours

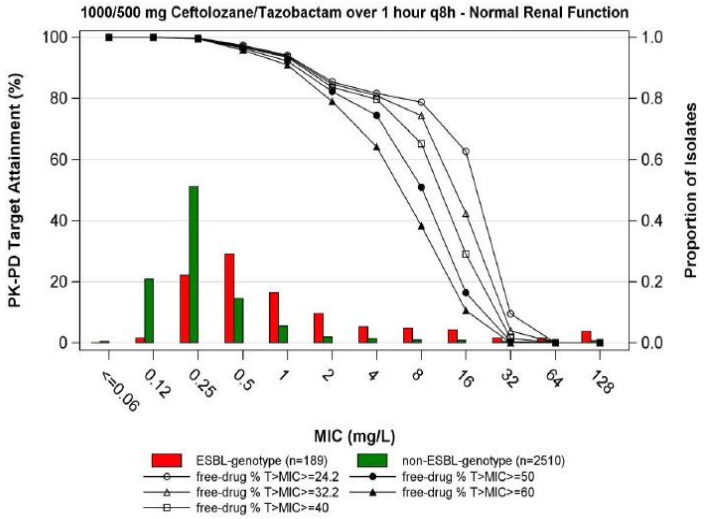


With regard to **tazobactam**, there is no widely accepted methodology for identifying the dose regimen. For the assessment of PTA taking into account MICs observed in Phase 3 isolates the tazobactam target of free-drug %T> threshold of 65.9% was evaluated, which was correlated with stasis in an in-vitro PD model (chemostat). Modelling for the ESBL-negative isolates was identical to that for ceftolozane alone. For ESBL-positive isolates, a multi-step, sequential algorithm was used to assess PTA by MIC value for each ceftolozane/tazobactam dosing regimen in each of the renal function categories defined above. Based on these analyses and on MICs for the Phase 3 isolates the figure below shows the PTA in relation to the MIC histograms for patients with normal renal function.

With a ceftolozane/tazobactam regimen of 1g/0.5 g q8h at least 80% or greater simulated subjects with normal renal function were predicted to achieve the free-drug target for net bacterial stasis up to an MIC of 8 µg/mL and to achieve the target for 1-log CFU reduction up to an MIC of 4 µg/mL. However, 90% or more PTA occurs only at MICs of 1 mg/L or less.

Figure 11

Figure 41: Percentage of Simulated Subjects Achieving Free-Drug %T>MIC Targets for Ceftolozane and Tazobactam Overlaid on Enterobacteriaceae (ESBL+ and ESBL-) Histograms from the Phase 3 Clinical Trials



In the UTI study, 14% of ME patients had molecularly confirmed ESBL-producing baseline pathogens. Of the 117 *Enterobacteriaceae* characterised 71% had at least a CTX-M-14 or CTX-M-15 enzyme.

Table 18

Tal linical and Microbiological Success by Susceptibility Interpretive _riteria Breakpoint Analysis for cUTI Pathogens (ME at TOC)

Pathogen	Clinical Success (n/N, %)				Microbiological Eradication (n/N, %)			
	At MIC values ≤8 µg/mL		At MIC values ≥16 µg/mL		At MIC values ≤8 µg/mL		At MIC values ≥16 µg/mL	
Enterobacteriaceae	289/297	97.3	9/9	100	263/297	88.6	5/9	55.5
E. coli	244/251	97.2	2/2	100	223/251	88.8	1/2	50.0
K. pneumoniae	21/21	100	2/2	100	18/21	85.7	2/2	100
P. mirabilis	10/10	100	NA	NA	10/10	100	NA	NA
P. aeruginosa	3/3	100	3/3	100	2/3	66.7	3/3	100
E. faecalis	NA	NA	14/15	93.3	NA	NA	5/15	33.3

In the cIAI study cure rates for 58 ESBL-positive pathogens in the MITT dataset were 25/29 (86.2%) for ceftolozane-tazobactam vs. 24/29 (82.8%) for meropenem. Cure rates for *E. coli* with CTX-M-14 or CTX-M-15 ESBLs were 9/11 (81.8%) and 8/11 (72.7%), respectively.

Table 19

Table 124: Clinical Success by Susceptibility Interpretive Criteria Breakpoint Analysis for cIAI Pathogens (MITT population)

Pathogen	Clinical Success (n/N, %)			
	MIC values ≤8 µg/mL		MIC values ≥16 µg/mL	
Enterobacteriaceae	353/422	83.6	6/11	54.5
Citrobacter freundii	10/14	71.4	NA	NA
Escherichia coli	260/307	84.7	2/4	50.0
Klebsiella oxytoca	17/22	77.3	NA	NA
Klebsiella pneumoniae	32/43	74.4	2/3	66.7
Proteus mirabilis	11/13	84.6	1/1	100
Enterobacter cloacae	26/33	78.8	2/4	50.0
Pseudomonas aeruginosa	30/43	69.8	NA	NA
Streptococcus anginosus	36/49	73.5	2/2	100
Streptococcus constellatus	25/32	78.1	NA	NA
Streptococcus salivarius	11/14	78.6	NA	NA
Bacteroides fragilis	51/56	91.1	2/2	100
Bacteroides thetaiotaomicron	2/3	66.7	19/22	86.4
Bacteroides ovatus	27/33	81.8	24/27	88.9
Bacteroides vulgatus	8/9	88.9	5/7	71.4

In a 1994 study, Payne *et al*. reported the inhibition of tazobactam against 35 beta lactamases (20 ESBLs and 15 conventional spectrum enzymes). The IC_{50} values demonstrated that tazobactam effectively inhibited most enzymes tested, with values below 1 µM for most Class A enzymes tested, including TEMs, SHVs and OXAs. More recent data demonstrate that for CTX-M-14 and CTX-M-15 there are nanomolar IC_{50} values for tazobactam. Tazobactam concentrations of 1 µM can be achieved in plasma with >99% probability for >20% of the dose interval at the proposed dose in infected patients.

Table 20

Ta **IC_{50}s of β-lactamase inhibitors for 35 plasmid-mediated β-lactamases**

β-lactamase	IC_{50} (µM)		
	Clavulanic acid	Sulbactam	Tazobactam
S. aureus Russell	0.28	26	2.3
TEM-1	0.09	6.1	0.04
TEM-2	0.18	8.7	0.05
SHV-1	0.03	17	0.14
TEM-3	0.03	0.03	0.01
TEM-5	0.03	1.2	0.28
TEM-6	0.12	0.45	0.17
TEM-7	0.1	0.62	0.18
TEM-9	0.29	0.9	0.34
TEM-10	0.03	0.34	0.08
SHV-2	0.05	2.8	0.13
SHV-3	0.04	2.7	0.1
SHV-5	0.01	0.63	0.08
Enzyme A	0.09	0.48	0.07
Enzyme B	0.01	0.12	0.01
Enzyme C	0.33	10	0.09
Enzyme D	0.04	0.57	0.01
Enzyme E	0.09	3.6	0.11
TEM-E1	0.05	0.64	0.02
TEM-E2	0.09	1.6	0.05
TEM-E3	0.02	0.2	0.06
TEM-E4	0.06	0.79	0.04
CAZ-3	0.13	2.5	0.06
DJP-1	0.01	0.21	0.02
TLE-1	0.11	5.5	0.05
MJ-1	0.09	40	0.43
PSE-4	0.15	3.7	0.1
BRO-1	0.02	0.02	0.02
OXA-1	1.8	4.7	1.4
OXA-2	1.4	0.14	0.01
OXA-4	8.4	16	5.6
OXA-5	3.1	18	0.25
OXA-6	1.6	51	1.7
OXA-7	0.36	40	0.61
PSE-2	0.81	37	0.94

Table 21

Ta **Concentration of β-lactamase Inhibitor Required to Reduce the Enzyme Activity by 50%**

	IC_{50} (µM)[a]		
Enzyme	Clavulanic Acid	Sulbactam	Tazobactam
TEM-1	0.143 ± 0.015	0.223 ± 0.017	0.002 ± 0.0001
CTX-M-15	0.037 ± 0.002	0.335 ± 0.063	0.003 ± 0.0002
CTX-M-14	0.120 ± 0.010	0.438 ± 0.077	0.004 ± 0.0001

[a]Post 5-minute Enzyme Inhibitor Preincubation

Table 22

Tal **Inhibition of β-lactamases by clavulanic acid, tazobactam, and sulbactam**

Enzyme	IC_{50} (nM)		
	Clavulanic acid	Sulbactam	Tazobactam
TEM-1	90	900	97
TEM-9	9[a]	270[a]	77
TEM-10	4.4[b]	940[b]	87
TEM-26	8.4	350	77
E104K/R164S	6.2	320	63

Table 23

Table 9: Inhibition of selected β-lactamases by β-lactamase inhibitors

Enzyme	Bush group*	IC_{50} (nM)		
		Clavulanate	Sulbactam	Tazobactam
Class A				
PC1	2a	30	80	27
TEM-1[c]	2b	90	900	97
TEM-2	2b	22	2,400	17
TEM-3	2b'	11	21	5
TEM-9[c]	2b'	9	270	77
TEM-10[c]	2b'	4.4	940	87
TEM-26[c]	2b'	8.4	350	77
SHV-1	2b	12	12,000	150
Class C				
P99	1	>100,000	5,600	8.5
S2	1	51,000	5,200	6,000
Class B				
CcrA	3	>500,000	>500,000	400,000
Sme-1	3	14,000	3,300	3,000
L1	3	>400,000	>400,000	>400,000

Note: The enzyme and inhibitor were preincubated for 10 min before substrate addition.

A further analysis of isolates obtained during the Phase 3 cUTI and cIAI studies showed that ESBL-producing isolates expressed a range of enzymes including CTX-M-14, CTX-M-15, CTX-M-27, OXA-1/30, OXA-10, TEM 1, TEM-176, SHV-1, SHV-11, and SHV-32 with many pathogens expressing more than one β-lactamase. The majority (65.2%) of ESBL enzymes identified in both *E. coli* and *K. pneumoniae* were CTX-M-14 and CTX-M-15.

In cUTI studies, the CTX-M-14/15 subpopulation of *E. coli* had ceftolozane/tazobactam MIC values ranging from 0.25 to >64 mg/L with the majority of MIC values between 0.25 and 1 mg/L (N=27). Clinical cure and eradication rates were high for patients with CTX-M-14/15 producing isolates with MIC values ≤ 1 µg/mL. Clinical and microbiologic success was recorded for 3 patients with *E. coli* isolates with MIC values ≥ 2 mg/L (2, 8 and > 64 mg/L). For the CTX-M-14/15 subpopulation of *K. pneumoniae*, the ceftolozane/tazobactam MIC values ranged from 0.25 mg/L to 32 mg/L and eradication and cure rates were comparable at all MIC values, though there were generally only single isolates at each MIC value. Clinical cure or microbiological eradication by MIC was not predictive for the presence of a CTX-M-15 *K. pneumoniae* isolate.

Table 24

Table 2: Summary of ESBL and Carbapenemase Positive *E. coli* and *K. pneumoniae* Identified in the Phase 3 cUTI Study

Organism	Genotype	N	Ceftolozane/tazobactam MIC Range (mg/L)
Escherichia coli	**Any CTX-M-15**	**53**	**0.25-8**
	CTX-M-15 only	7	0.25-1
	CTX-M-15, OXA-1/30	27	0.25-8
	CTX-M-15, TEM	6	0.25-0.5
	CTX-M-15, OXA-1/30, TEM	12	0.25-8
	CTX-M-15, CTX-M-27	1	0.5
	Any CTX-M-14	**12**	**0.25-1**
	CTX-M-14 only	4	0.25-1
	CTX-M-14, TEM-1	8	0.25-0.5
	Other CTX-M	**12**	**0.25-2**
	Alone	5	0.25-1
	With TEM	7	0.25-2
	SHV or TEM	**11**	**0.12-1**
	Carbapenemase	**2**	**8->64**
	NDM-5, CTX-M-15, OXA-1/30, TEM-1	1	>64
	KPC-2, TEM-1	1	8
Klebsiella pneumoniae	**Any CTX-M-15**	**17**	**0.25->64**
	CTX-M-15, OXA, SHV	2	0.5-8
	CTX-M-15, OXA, SHV, TEM	15	0.25->64
	Other ESBL	**5**	**1-8**

cUTI=complicated urinary tract infection; ESBL=extended spectrum β-lactamase; MIC=minimum inhibitory concentration

In the cIAI studies, the ceftolozane/tazobactam MIC values ranged from 0.25 to 4 mg/L for CTX-M-14/15 subpopulation of *E. coli* baseline pathogens. All subjects with a CTX-M-14/15 positive *E. coli* were clinical cures. It is notable that the presence or absence of CTX-M-14/15 did not correlate with any change in clinical cure rates compared with the general *E. coli* population. For the CTX-M-14/15 subpopulation of *K. pneumoniae,* the ceftolozane/tazobactam MIC values ranged from 1 to 16 mg/L. All subjects with a CTX-M-14/15 positive *K. pneumoniae* were classified as clinical cure. High clinical cure rates were associated with MIC values ≤ 8 mg/L.

Table 25

Ta Summary of ESBL positive *E. coli* and *K. pneumoniae* identified in the Phase 3 cIAI Study

Organism	Genotype	N	Ceftolozane-tazobactam MIC Range (mg/L)
Escherichia coli	**Any CTX-M-15**	**26**	**0.25-64**
	CTX-M-15 only	2	0.25-2
	CTX-M-15, OXA-1/30	8	0.25-32
	CTX-M-15, TEM	7	0.25-64
	CTX-M-15, OXA-1/30, TEM	9	1-4
	Any CTX-M-14	**5**	**0.5-2**
	CTX-M-14, TEM-1	5	0.5-2
	Other CTX-M	**5**	**0.25-0.5**
	OXA-1/30	**3**	**0.25-16**
	TEM	**17**	**0.12->64**
	SHV and TEM	**1**	**0.25**
Klebsiella pneumoniae	**Any CTX-M-15**	**8**	**1->64**
	CTX-M-15, OXA-1/30, SHV	1	4
	CTX-M-15, OXA-1/30, SHV, TEM	7	1->64
	SHV +/- TEM	**6**	**0.25-64**

cIAI=complicated intraabdominal infection; ESBL=extended spectrum β-lactamase; MIC=minimum inhibitory concentration

It should be noted that the applicant has chosen a higher dose of ceftolozane/tazobactam for treatment of VAP (2 g/1 g q8h). In the applicant's summary it is stated that results of the PD target attainment analyses for this 2 g/1 g ceftolozane/tazobactam q8h regimen in normal renal function and dosing regimens adjusted for renal function, which are based on the same nonclinical PD targets as described above, resulted in robust target attainment for MIC values approximately one-doubling

dilution step higher relative to the analyses for the 1 g/ 0.5 g regimen and adjustments for renal function.

Effects on cardiac conduction

In a TQT study (CXA-QT-10-02) in 52 male and female adults, testing therapeutic (1g/0.5g) and supra-therapeutic (3g/1.5g) doses of CXA- TAZ showed very slight increases (i.e. > 2 ms) of the baseline-adjusted QTcI for the supratherapeutic dose group through about 3 h post-dose and a nearly flat response for the therapeutic dose group. There was no indication of a differential effect due to gender. No subject had a QTcI interval > 450 ms. One subject had values of QTcF > 450 ms following the 3 g / 1.5 g dose on a day when the baseline QTcF was 445 ms and the post-dose values ranged from 451 to 453 ms at 0.5, 1.0 and 16.5 hours post-dose.

Study CXA-101-MD-11-07 included a further assessment of cardiac repolarization at the higher doses envisaged for certain types of infection (Ceftolozane-tazobactam 2g/ 1g q8h). The individually corrected QTc change from the pre-dose baseline using the Fridericia formula (QTcF = QT/RR0.33) on study Day 5 was the primary parameter for analysis. The primary endpoint analysis was determined by subtracting the baseline-adjusted placebo group from the baseline-adjusted 3g group to obtain the so-called double-delta. This revealed insignificant differences at each time point vs. placebo after 5 days of dosing.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Ceftolozane appears to have straightforward PK in humans, which is characterised by low protein binding, dose proportionality up to 3 g doses, relatively low intra- and inter-subject variability and predominance of urinary excretion of unchanged drug. Distribution is into the extracellular compartment, including the ELF. In subjects with normal renal function the elimination half-life is short (~2.5-3 h) and independent of dose, so that accumulation was not observed after TID dosing for 10 days. The estimated CLr approximates to mean total plasma clearance and both parameters are directly related to CrCL.

Co-administration of tazobactam (0.5 g q8h) with ceftolozane (1 g q8h) did not show an effect of ceftolozane on tazobactam and there were only small increases in ceftolozane AUC. On co-administration with ceftolozane the elimination half-life of tazobactam is around 1 h and there is no accumulation after 1 g q8h dosing for 10 days. Tazobactam has low binding to plasma proteins, distributes mainly into extracellular fluid with similar penetration into ELF as ceftolozane and is eliminated by glomerular filtration and tubular secretion involving OCT1 and OCT3. The plasma CL and CLr for tazobactam increase with increasing CrCL but some elimination is via conversion to the ring-open form (M-1). After multiple doses, around 70% of the tazobactam dose appears in urine unchanged.

The pharmacologically inactive metabolite of tazobactam (M-1) has a longer t½ of 3-4 h, suggestive of rate-limited elimination, which is not affected by co-administration with ceftolozane. As a result, M-1 shows modest accumulation following repeated dosing with a median AI of <2-fold. However, on day 10 of q8h dosing with 1 g/0.5 g of the combination the AUC for M-1 was about 5% of that for parent drug. M-1 plasma concentrations increase when renal function is impaired.

Due to the lack of Phase 3 PK data the final POPPK analysis was based on Phase 1 and 2 data only. As expected, CrCL was the most significant covariate affecting the PK of ceftolozane and tazobactam. The model did not identify any baseline covariates that would require dose adjustment other than

moderate or more severe degrees of renal impairment. The final models showed that presence of bacterial infection affected PK of ceftolozane and tazobactam, albeit to a minor or modest extent. Ceftolozane CL was higher in patients with infections and Vd was increased for both actives, particularly in IAI. As a result ceftolozane exposure is decreased by 20% in the presence of infection while tazobactam is unaffected.

Based on accumulated non-clinical and clinical data the omission of in-vitro metabolism studies and a clinical mass balance study with ceftolozane alone and/or with the combination is accepted. In addition, taking into account the low protein binding, omission of a study in hepatic impairment is accepted. Based on the Phase I data in subjects with renal impairment and on the POPPK models the applicant has derived dose adjustment criteria not only for moderate impairment (which was implemented in Phase 3 studies) but also for severe impairment and ESRD, with and without HD. The available PK data support the proposals made in the SmPC.

The potential for DDIs to occur seems to be relatively low.

Overall, the approach to assessment of PK for ceftolozane and tazobactam/M-1 has been appropriate, with caveat that absence of PK data from patients in Phase 3 studies hampers to support confirmatory PK/PD and exposure-response analyses in infected patients.

Pharmacodynamics

The rationale for addition of tazobactam to form this FDC relies on its ability to protect ceftolozane from hydrolysis by some bacterial beta-lactamases produced by non-pseudomonal aerobic Gram-negative organisms. However, it cannot be assumed that the dose of tazobactam that is approved for use with piperacillin is also appropriate for use with ceftolozane. Therefore it is essential that the data support adequacy of the tazobactam dose to inhibit common ceftolozane-hydrolysing enzymes. However, there is no well-established PK-PD methodology for identifying dose regimens for beta-lactamase inhibitors.

The following points were taken into account for tazobactam dose selection:

- There is a concentration-dependent effect of tazobactam on the activity of ceftolozane in the presence of beta-lactamases that can hydrolyse ceftolozane but are inhibited by tazobactam.
- Hyper-production of beta-lactamases normally inhibited by tazobactam may result in failure of tazobactam at the usual clinical dose to protect ceftolozane from hydrolysis.
- The %T>threshold appears to be the important factor for efficacy of tazobactam.
- The non-clinical data indicate that the tazobactam thresholds vary by species and enzyme. Derivation of the %T>threshold targets predicted to be associated with stasis and 1-log or 2-log kill was based on very limited strains and enzymes. Different PD targets were estimated from the in-vivo neutropenic mouse thigh (NMT) infection model and from in-vitro chemostat models. The applicant finally focused on the lowest estimate, which was that obtained from the NMT model, stating that the in-vitro chemostat PD driver (½ MIC) for tazobactam was not consistent with other experiments that attempted to identify tazobactam thresholds.

In relation to the Marketing Authorisation application, the following observations are made:

1. In light of the indications studied it is not agreed that the clinical data support the adequacy of the tazobactam dose. This is because cIAI are mainly treated surgically, with adjunctive use of antibacterial agents and because cUTI is not a test of the adequacy of the dose when tazobactam, like ceftolozane, is mainly excreted renally, reaching high urinary concentrations.

2. The applicant has stated that *these results confirm the sufficiency of tazobactam exposure for efficacy against many Class A β-lactamase enzymes*. The important point is that the 500 mg q8h dose is likely not sufficient, or is at least borderline, even for some Class A enzymes, especially if they are being produced in large amounts by certain species.

3. It is very difficult to adequately convey in the SmPC the limitations of tazobactam, in terms of range of enzymes inhibited and the fact that the dose may not suffice in case of hyper-production of beta-lactamases.

4. Among the target pathogens for ceftolozane, tazobactam only contributes to the overall activity of ceftolozane against *Enterobacteriaceae*. Even against these species, tazobactam has several very important gaps in its inhibitory spectrum. There has to be considerable concern that many users of Zerbaxa will not appreciate its limitations, with a risk that it will be used empirically during the first and vital 24-48 h of therapy against organisms that are later confirmed to be resistant.

Overall, the PK-PD justification for the tazobactam dose is not considered to be robust. Data shown above (Figure 11) however suggests that provided the susceptibility breakpoint for enterobacteria is no more than 1 mg/L, the tazobactam dose may suffice to cover the majority of the common Class A enzymes.

2.4.5. Conclusions on clinical pharmacology

The adequacy of the tazobactam dose in the FDC has been poorly justified. Nevertheless, the CHMP accepts that provided the susceptibility breakpoint for enterobacteria is no more than 1 mg/L, the tazobactam dose may suffice to cover the majority of the common Class A enzymes. Since this is the EUCAST-recommended breakpoint for enterobacteria it seems possible to accept the tazobactam dose.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose ranging studies were performed. The dose of ceftolozane/tazobactam (1.5 g every 8 hours) in the Phase 3 cUTI and cIAI trials was selected based on a comprehensive PK/PD analysis.

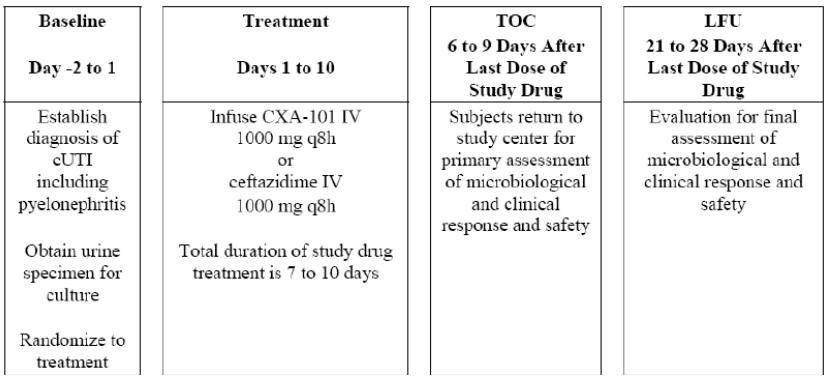
In addition, the results of the Phase 2 studies in subjects with cUTI (CXA-101-03) and cIAI (CXA-10-01) were provided in support for the dose selected.

CXA-101-03

This was a randomised (2:1) double-blind study that compared ceftolozane 1g q8h vs. ceftazidime 1 g q8h for 7 days to 10 days in cUTI, including pyelonephritis. For non-catheterised patients an eligible baseline culture was to have 1 or 2 bacterial isolates at ≥ 10^5 CFU/mL each. Cultures with >2 isolates were considered contaminated unless one of the pathogens was simultaneously isolated from blood. For catheterized subjects the urine was considered contaminated if >1 isolate was present in any number unless one isolate at ≥ 10^5 was also present in blood. Patient selection criteria were similar to Phase 3.

Figure 12

F ıdy Design



Of the 127 treated patients > 90% completed the LFU visit. More ceftolozane patients had no uropathogen at baseline (23.5% vs. 9.3%) but more ceftazidime patients had no TOC culture (18.4% vs. 6.2%). The microbiological response rates were inconsistent between treatments in the two analysis populations. However, the failure rates were higher with ceftolozane in the mITT and ME populations.

Table 26

T crobiological Response at the Test of Cure Visit (mMITT and ME pulations)

	mMITT Population		ME Population	
Microbiologic Response, TOC	CXA-101 (N=65)	Ceftazidime (N=38)	CXA-101 (N=55)	Ceftazidime (N=27)
Cure Rate, n (%)	54 (83.1)	29 (76.3)	47 (85.5)	25 (92.6)
95% Confidence Interval	(71.7, 91.2)	(59.8, 88.6)	(73.3, 93.5)	(75.7, 99.1)
Failure Rate, n (%)	8 (12.3)	3 (7.9)	8 (14.5)	2 (7.4)
Indeterminate, n (%)	3 (4.6)	6 (15.8)	NA	NA

NA=not applicable; subjects with indeterminate responses were excluded from the ME population

The cure rates did not differ significantly by region but they were lower for patients with cUTI vs. those with pyelonephritis due to the recurrences. Results of cUTI versus pyelonephritis were not provided for the ME population in the study report.

Table 27

crobiological Response at the Test of Cure Visit by Geographic gions and Type of cUTI (mMITT Population)

Subgroup	Microbiologic Response, TOC	CXA-101 (N=65)	Ceftazidime (N=38)
Geographic Region			
US	Cure Rate, n/N (%)	7/8 (87.5)	2/2 (100.0)
	95% Confidence Interval	(47.3, 99.7)	(15.8, 100.0)
Europe	Cure Rate, n/N (%)	47/57 (82.5)	27/36 (75.0)
	95% Confidence Interval	(70.1, 91.3)	(57.8, 87.9)
cUTI Diagnosis			
cLUTI	Cure Rate, n/N (%)	36/44 (81.8)	19/26 (73.1)
	95% Confidence Interval	(67.3, 91.8)	(52.2, 88.4)
Pyelonephritis	Cure Rate, n/N (%)	18/21 (85.7)	10/12 (83.3)
	95% Confidence Interval	(63.7, 97.0)	(51.6, 97.9)

Both agents were highly effective against *E. coli.* Two ceftolozane patients had baseline uropathogens that were resistant to the drug based on MICs ≥32 µg/mL and both (one with *S. aureus* and one with *E. cloacae*) were microbiological failures at TOC (although the latter was a clinical cure at TOC).

Table 28

Ta crobiological Eradication Rates at the Test of Cure Visit (mME Population)

Baseline Uropathogen	CXA-101 (N=55) n/N (%)	Ceftazidime (N=27) n/N (%)
Gram-Negative Bacteria (aerobes)	**47/53 (88.7)**	**22/24 (91.7)**
Escherichia coli	33/36 (91.7)	18/19 (94.7)
Pseudomonas aeruginosa	3/5 (60.0)	0/0 (0.0)
Klebsiella pneumoniae	3/3 (100.0)	1/1 (100.0)
Proteus mirabilis	2/2 (100.0)	1/2 (50.0)
Enterobacter cloacae	2/3 (66.7)	0/0 (0.0)
Enterobacter aerogenes	1/1 (100.0)	2/2 (100.0)
Citrobacter freundii	1/1 (100.0)	0/0 (0.0)
Klebsiella oxytoca	1/1 (100.0)	0/0 (0.0)
Serratia marcescens	1/1 (100.0)	0/0 (0.0)
Gram-Positive Bacteria (aerobes)	**0/2 (0.0)**	**3/3 (100.0)**
Enterococcus faecalis	0/1 (0.0)	1/1 (100.0)
MSSA	0/1 (0.0)	1/1 (100.0)
Streptococcus agalactiae	0/0 (0.0)	1/1 (100.0)

The 8 (12.3%) failures on ceftolozane and 3 (7.9%) on ceftazidime tended to be older than the overall mMITT population and 9/11 had cLUTI. Five of the 11 had *E. coli* as the baseline and persisting pathogen. None of the pathogens from 4 ceftolozane failures with baseline and post-baseline susceptibility test results developed resistance. Overall, 7/11 patients were clinical cures at TOC.

The clinical response rates were slightly higher than the microbiological response rates, especially among subjects with cLUTI, reflecting asymptomatic bacteriuria detected at the TOC visit. The concordance rate between microbiological and clinical response at TOC in the mMITT population was 83.1% (54/65) in the ceftolozane group and 84.2% (32/38) in the ceftazidime group.

Table 29

T: linical Response at the Test of Cure Visit (mMITT and ME r opulations)

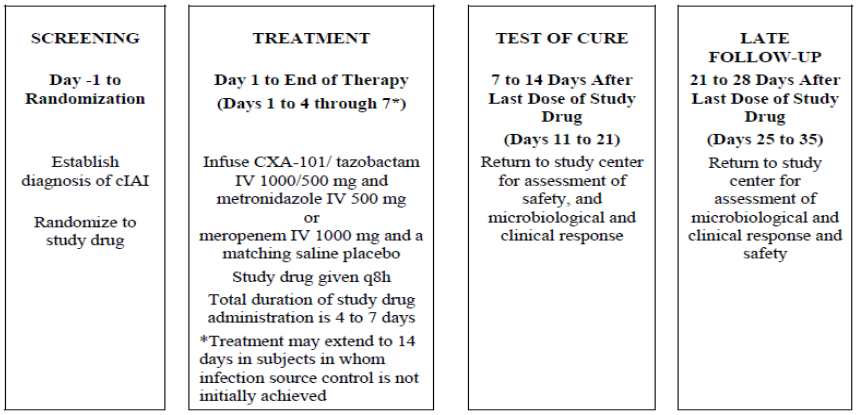
	mMITT Population		ME Population	
Clinical Response, TOC	CXA-101 (N=65)	Ceftazidime (N=38)	CXA-101 (N=55)	Ceftazidime (N=27)
Cure Rate, n (%)	59 (90.8)	35 (92.1)	51 (92.7)	27 (100.0)
95% Confidence Interval	(81.0, 96.5)	(78.6, 98.3)	(82.4, 98.0)	(87.2, 100.0)
Failure Rate, n (%)	4 (6.2)	1 (2.6)	4 (7.3)	0 (0.0)
Indeterminate, n (%)	2 (3.1)	2 (5.3)	NA	NA

NA=not applicable; subjects with indeterminate responses were excluded from the ME population

- There were six patients with E. coli in blood of which 3 in the ceftolozane group had documented eradication.
- There were 4 new infections with non-susceptible E. faecalis in the ceftolozane group. One patient per treatment group had a superinfection - C. albicans in the ceftolozane patient and E. faecalis in the ceftazidime patient.
- The sustained clinical cure rates at the LFU visit were 98.0% for ceftolozane and 92.6% for ceftazidime. Microbiological recurrence was uncommon (7.0% and 14.0%).

CXA-IAI-10-01

This was a double-blind study in IAI that compared 4-7 days (but up to 14 days was allowed if needed) of ceftolozane-tazobactam 1g/0.5g q8h with metronidazole (at 500 mg q8h, used at the investigators discretion in upper GI infection and community based cholecystitis) vs. meropenem 1 g q8h using 2:1 randomisation and stratification by primary site of infection (localised complicated appendicitis vs. other sites of IAI). Hospitalisation was mandatory for at least the first 9 doses (approximately 3 days).



Eligible patients had one of the following conditions with evidence of intra-peritoneal infection:

a. Cholecystitis with progression of the infection beyond the gallbladder wall

b. Diverticular disease with perforation or abscess

c. Appendiceal perforation or peri-appendiceal abscess

d. Acute gastric or duodenal perforation if operated on > 24 h post-event

e. Traumatic perforation of the intestine if operated on > 12 h post-event

f. Peritonitis due to perforated viscus, postoperative or spread from other focus of infection

g. Intra-abdominal abscess (including liver and spleen).

Patients had to require surgical intervention within 24 h before or after the first dose of study drug.

There were 121 patients randomised and treated (including 82 ceftolozane-tazobactam), of which > 90% completed treatment and the LFU visit. The mMITT population comprised 86 patients (61 and 25 per treatment group). The most common diagnosis was appendiceal perforation or peri-appendiceal abscess reported in 49% followed by cholecystitis and diverticular disease. No subjects had bacteraemia at baseline.

For the primary analysis of clinical cure at the TOC visit in each of the mMITT and ME populations the cure rates were lower for ceftolozane-tazobactam.

Table 30

Table 11-5: Clinical Response at the Test of Cure Visit (mMITT and ME Populations)

	mMITT Population		ME Population	
Clinical Response, TOC	CXA-101/ Tazobactam (N=61)	Meropenem (N=25)	CXA-101/ Tazobactam (N=53)	Meropenem (N=24)
Clinical Cure Rate, n (%)	51 (83.6)	24 (96.0)	47 (88.7)	23 (95.8)
95% Confidence Interval	(71.9, 91.8)	(79.6, 99.9)	(77.0, 95.7)	(78.9, 99.9)
Clinical Failure Rate, n (%)	6 (9.8)	1 (4.0)	6 (11.3)	1 (4.2)
Indeterminate, n (%)	4 (6.6)	0 (0.0)	NA	NA

NA=not applicable; subjects with indeterminate responses were excluded from the ME population

The larger treatment difference in the mMITT population was ascribed to 4 indeterminate patients in the ceftolozane-tazobactam group who were excluded from the ME population. There were 6 vs. 1 failures with features summarised below.

Table 31

T erview of Clinical Failures (mMITT Population)

Subject ID	Age, Race Gender[a]	APACHE II [BL CrCl][b]	Diagnosis	Baseline Pathogen	Duration of Treatment/ Time to Failure (days)	Reason for Clinical Failure	Microbiological Outcome
CXA-101/tazobactam Group							
7103 IA051	51 W F	9 [76.7]	Appendix, spontaneous rupture	*E. coli* *S. anginosus*[e]	7/7	Post-surgical wound infection	Persistence
7302 IA011	26 W M	10 [157]	Appendix, spontaneous rupture	*E. coli* *B. fragilis*[e]	7/13	Post-surgical wound infection[c]	Persistence
7302 IA029	35 W F	8 [118]	Inter-intestinal abscess due to diverticular perforation (multiple abscesses)	*E. coli*	7/7	Persistent/ recurrent infection[d]	Persistence
7302 IA052	43 W F	7 [71.3]	Diverticular disease, spontaneous rupture	*E. coli* *E. cloacae* *B. fragilis*	7/7	Treatment with additional antibiotics	Presumed Persistence
9305 IA105	40 B M	4 [186.7]	Acute gastric/duodenal perforation (single abscess)	*Prevotella buccae*	6/6	Treatment with additional antibiotics	Presumed Persistence
9306 IA049	60 W F	8 [114.1]	Peritonitis due to perforated colon (malignancy)	*E. coli* *S. anginosus*	7/9	Persistent/recurrent infection	Eradication
Meropenem Group							
7302 IA050	54 W M	7 [71.6]	Appendix, spontaneous rupture	*E. coli*	7/7	Treatment with additional antibiotics	Presumed Persistence

Higher cure rates were observed for meropenem within each country, except one 83% in both groups). Clinical responses at TOC were similar for low-risk and high-risk subjects (latter included the elderly, those with higher APACHE II scores and/or decreased renal function). Clinical outcomes in both treatment groups were somewhat higher for subjects with a primary diagnosis of localised complicated appendicitis vs. other sites.

In the ME population microbiological success was observed in 90.6% ceftolozane-tazobactam and 95.8% meropenem patients.

In the CE population the clinical cure rates at TOC were rather more comparable between groups.

Table 32

Table 11-8: Clinical Response at the Test of Cure Visit (CE and Expanded ME Populations)

	CE Population		Expanded ME Population	
Clinical Response, TOC	CXA-101/ Tazobactam (N=70)	Meropenem (N=35)	CXA-101/ Tazobactam (N=56)	Meropenem (N=24)
Clinical Cure Rate, n (%)	64 (91.4)	33 (94.3)	50 (89.3)	23 (95.8)
95% Confidence Interval	(82.3, 96.8)	(80.8, 99.3)	(78.1, 96.0)	(78.9, 99.9)
Clinical Failure Rate, n (%)	6 (8.6)	2 (5.7)	6 (10.7)	1 (4.2)

Clinical and microbiological outcomes against the common Gram-negative aerobic pathogens (including *E. coli, K. pneumoniae* and *P. aeruginosa*) were generally comparable between treatments but the clinical cure rates for Gram-negative anaerobes were 72.7% for ceftolozane-tazobactam vs. 100% for meropenem.

Clinical relapse was uncommon (3%) in both treatment groups and there were no microbiological recurrences at the LFU visit. Three patients had emergent infections in the ceftolozane-tazobactam group, all associated with Gram-positive aerobes (*E. avium, E. faecium* and *Staphylococcus aureus, E. faecalis*).

2.5.2. Main studies

The applicant initiated two Phase 3 studies in each of the two claimed indications. After obtaining agreement from the CHMP the applicant proceeded with a single study for each of the two (cUTI and cIAI) indications by pooling data from the 2 respective identical Phase 3 cUTI and cIAI protocols.

Both integrated phase 3 studies were multicentre prospective, randomised, double-blind, and included male and female adult subjects (> 18 years of age) requiring intravenous treatment; patients with underlying immuno-compromising illnesses and/or those on immunosuppressant therapies were excluded, as were patients with severe or rapidly progressing disease such as septic shock, or those not expected to survive the 4-5 week study period. Subjects with severe renal impairment (CLCR <30 mL/min) and significant laboratory abnormalities were also excluded.

CXA-cUTI-10-04-05:
A Multicentre, Double-Blind, Randomised, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam and Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis

Methods

Study Participants
Eligible adults had a diagnosis of cUTI or pyelonephritis and met the following inclusion criteria:

- Pyuria (WBC count >10/μL in unspun urine or ≥10 per high power field in spun urine).
- Clinical signs and/or symptoms of cUTI, either of:

  a. Pyelonephritis, as indicated by ≥ 2 of the following OR complicated lower UTI, as indicated by ≥ 2 of the following new or worsening symptoms of cUTI:
     - Documented fever (oral temperature >38°C) accompanied by subject symptoms of rigors, chills, or "warmth";
     - Flank pain (for pyelonephritis); Suprapubic pain or flank pain (for cUTI)
     - Costovertebral angle tenderness or suprapubic tenderness on physical exam or
     - Nausea or vomiting
     - Dysuria; urinary frequency, or urinary urgency (for cUTI only)

  b. Plus, for cUTI, at least 1 of the following complicating factors:

- Males with documented history of urinary retention;
- Indwelling urinary catheter, scheduled to be removed before the EOT;
- Current obstructive uropathy, scheduled to be medically or surgically relieved before the EOT; or
- Any functional or anatomical abnormality of the urogenital tract (including anatomic malformations or neurogenic bladder) with voiding disturbance resulting in at least 100 mL residual urine.

Pre-treatment baseline urine culture specimens were obtained within 24 h before the first dose of study drug. Subjects were enrolled before the Investigator knew the results of the baseline urine culture. No potentially effective antibacterial agents were allowed within 48 h prior to obtaining the baseline urine specimen.

In non-catheterised subjects at least 1 and not more than 2 bacterial isolates at $\geq 10^5$ CFU/mL each was required to qualify. If more than 2 bacterial isolates were identified, the culture was considered contaminated, unless 1 of the isolates that grew in the urine at $\geq 10^5$ CFU/mL was also isolated from a blood culture at the same visit.

In catheterised subjects a culture that grew >1 organism at any colony count was considered contaminated unless 1 of the isolates that grew in the urine at $\geq 10^5$ CFU/mL was also isolated from a blood culture at the same visit. Local or regional laboratory urine culture results were used to determine subject eligibility.

Treatments

Subjects received (1:1 randomisation; block randomisation was used, stratified by investigational site) ceftolozane/tazobactam 1.5 g q8h over 1 h or levofloxacin 750 mg QD over 1.5 h for a fixed duration of 7 days but with an allowance for up to 9 days in case of removal of an indwelling catheter, recent bladder instrumentation or treatment for a urinary tract obstruction. The dose was adjusted in case of moderate renal insufficiency and discontinued if CrCL fell to < 30/ml/min.

Objectives

The primary objective was to demonstrate non-inferiority of ceftolozane/tazobactam vs. levofloxacin for microbiological eradication in the ME population at TOC (7 days [± 2 days] post-treatment based on a margin of 10% at a 1-sided 0.005 significance level. The comparison of eradication rates in the microbiological modified intent-to-treat (mMITT) population was secondary. Microbiological "eradication" was defined as all baseline infecting pathogen(s) at $<10^3$ CFU/mL.

Outcomes/endpoints

Central laboratory urine analysis was carried out on days -1, 3, at EOT, TOC and LFU. Further (local lab) analyses were carried out on study days 2 and 4-7 as indicated.

Definitions of per-pathogen microbiological outcomes were:
Eradication (EOT, TOC): All baseline infecting pathogen(s) at $<10^3$ CFU/mL

Presumed eradication (EOT): No EOT urine culture but last known urine obtained on day ≥ 3 on study drug showed all infecting pathogen(s) at $<10^3$ CFU/mL

Persistence (EOT, TOC): $\geq 10^3$ CFU/mL of any baseline pathogen; persistence at EOT was carried forward to TOC

Indeterminate (EOT, TOC): No interpretable urine culture available at EOT or TOC and no previous urine culture after ≥ 3 days of study drug that is negative (no growth)

Sustained Eradication (LFU): Urine obtained within the 21 to 42 days post-therapy window showed all baseline infecting pathogen(s) remained $<10^3$ CFU/mL

Recurrence (LFU): Urine taken any time after documented eradication at the TOC visit and up to the time of LFU with ≥10^3 CFU/mL of the baseline infecting pathogen(s)

Indeterminate (LFU): No urine culture obtained at LFU visit

Definitions of clinical outcomes:
Clinical Cure: Complete resolution or marked improvement in baseline signs and symptoms or return to pre-infection signs and symptoms without requirement for additional antibacterial therapy after EOT

Clinical Failure: Persistence of ≥1 signs or symptoms of infection or reappearance of or new signs and symptoms that require additional or alternative antibacterial therapy

OR AE leading to study drug discontinuation and need for non-study antibacterial therapy

OR clinical failure at the EOT that was carried forward to the TOC visit

Indeterminate: No evaluation of clinical outcome for any reason or outcome assessment confounded

Sustained cure: No evidence of resurgence of baseline signs and symptoms after EOT

Relapse: Signs and/or symptoms reappear between the TOC and LFU visits

Sample size
With 334 microbiologically evaluable patients randomised 1:1 the study had an overall power of ~80% in terms of the primary efficacy hypothesis. It was planned that 477 subjects per arm would be randomised across the consolidated CXA-cUTI-10-04 and CXA-cUTI-10-05 protocols assuming an evaluability rate of 70% and a response rate of 82.8%.

Randomisation
Randomisation (1:1) used IVRS/IWRS. Block randomisation was used, stratified by investigational site.

Blinding (masking)
The study was double-blind. An unblinded study site pharmacist or designee prepared and administered the study drug infusions.

Statistical methods
Due to the large number of investigational sites and small sample sizes expected per site, the primary and key secondary analyses were adjusted with the stratification factors of region and primary site of infection.

Study populations were defined as follows:

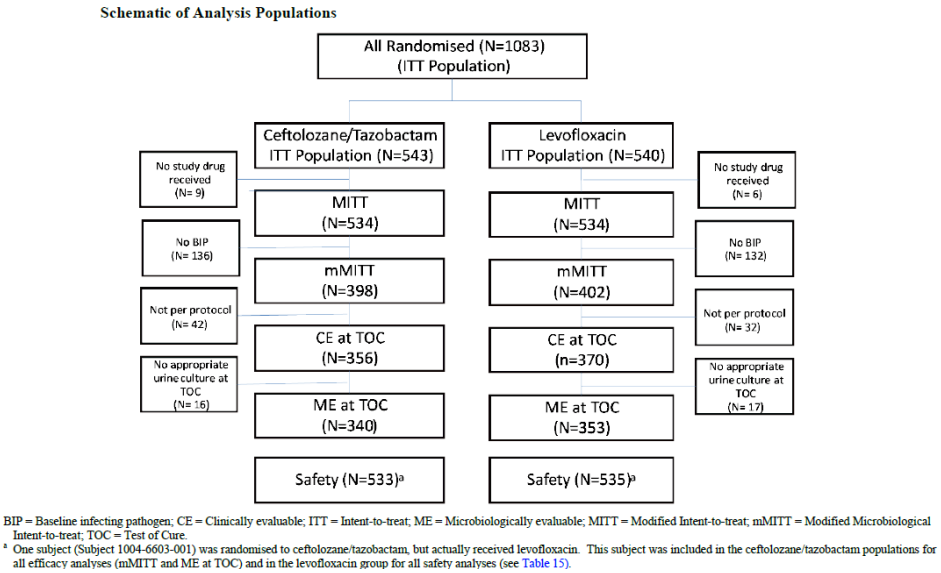
- ITT - all randomised
- Safety - all treated
- MITT- all randomised who received a dose of assigned therapy
- mMITT- all MITT with at least one qualified uropathogen at in baseline urine specimen
- CE at TOC - all mMITT who adhered to protocol, had a TOC visit within the specified visit window and had an outcome
- CE at LFU- all CE cures at TOC with LFU assessment or failed between TOC and LFU
- ME at TOC - all CE at TOC who had a urine culture with interpretable result at TOC
- ME at LFU - all ME successes at TOC with LFU assessment or failed between TOC and LFU

Results

Participant flow

In total 1083 were randomised and approximately 95% in both treatment arms completed the study, while 74.7% completed study drug. Around 25% of randomised patients were excluded from the mMITT as they had no qualifying baseline pathogen. Twelve patients who were not study failures received an active non-study antibacterial agent prior to TOC and were excluded from the ME and CE analysis populations.

Figure 13



BIP = Baseline infecting pathogen; CE = Clinically evaluable; ITT = Intent-to-treat; ME = Microbiologically evaluable; MITT = Modified Intent-to-treat; mMITT = Modified Microbiological Intent-to-treat; TOC = Test of Cure.

[a] One subject (Subject 1004-6603-001) was randomised to ceftolozane/tazobactam, but actually received levofloxacin. This subject was included in the ceftolozane/tazobactam populations for all efficacy analyses (mMITT and ME at TOC) and in the levofloxacin group for all safety analyses (see Table 15).

Recruitment

Around 75% of randomised subjects were enrolled in 123 sites in Europe. The remaining subjects were enrolled at 12 sites in South America, North America and the Rest of World.

Conduct of the study

After first subject enrolment, CXA-cUTI-10-04 and CXA-cUTI-10-05 were combined (Protocol version 3.0 1 April 2013). In a further amendment, CHMP-specific primary and key secondary efficacy objectives, variables, analysis populations and key analyses were included. Pooling across studies was based on identical protocols. The treatment effect by protocol for the ME at TOC was explored and was confirmed to be comparable.

A finding of GCP non-compliance with potential risk for data integrity was reported in a Sponsor audit, conducted after enrolment had closed at Site 5609 (6 patients). These 6 were excluded from the primary efficacy analysis and sensitivity analyses showed that this had no effect on the conclusions.

Baseline data

Baseline demographic characteristics of the ME and mMITT populations were comparable between treatment groups. The overall demographics of the study population reflected the fact that 81.8% of subjects had pyelonephritis so that only 18.2% had cUTI. Thus females of younger age range predominated. For example, in the ME population the mean age was 45 years and 81% were female

with mean CrCL 98 mL/min. In the cUTI population the mean age was 64 years, 61% were male and mean CrCL was 84 mL/min.

Outcomes and estimation

In the primary analysis non-inferiority was demonstrated. The 95% CI of the % difference between treatments did not span 1.0 and favoured ceftolozane-tazobactam. Non-inferiority was also demonstrated within the subset with acute pyelonephritis in the ME and mMITT populations and after exclusion of patients with levofloxacin-resistant pathogens.

Microbiological response rates in patients with cUTI in both treatment arms were lower vs. pyelonephritis but numerically higher for the test agent vs. levofloxacin even after exclusion of levofloxacin-resistant pathogens. The results of all sensitivity analyses were consistent with the primary outcome.

Table 33

Ta[illegible]licrobiological Response at TOC Visit by Overall Population and [illegible]ubgroups (ME at TOC Population)

Subgroup/Population Microbiological Response	Ceftolozane/Tazobactam n (%)	Levofloxacin n (%)	% Difference (95% CI)
Overall Population (Primary Analysis - ME at TOC)			
Overall Analysis	N=340	N=353	
Success	288 (84.7)	266 (75.4)	9.4 (1.54, 17.12)[a]
Failure	52 (15.3)	87 (24.6)	
Diagnosis			
Pyelonephritis	N=280	N=287	
Success	242 (86.4)	231 (80.5)	5.9 (-0.20, 12.04)
Failure	38 (13.6)	56 (19.5)	
cLUTI	N=60	N=66	
Success	46 (76.7)	35 (53.0)	23.6 (6.91, 38.47)
Failure	14 (23.3)	31 (47.0)	

In the mMITT population 57 (14.3%) in the ceftolozane/tazobactam group and 94 (23.4%) in the levofloxacin group were observed failures and cUTI cases predominated. Most of the microbiological failures were clinical successes and were considered to have asymptomatic bacteriuria.

Microbiological response rates for Gram-negative aerobes were higher with ceftolozane/tazobactam than with levofloxacin, reflecting the level of baseline resistance to the latter. In contrast few Gram-positive aerobes were eradicated in the ceftolozane/tazobactam group. Approximately 14% of ME patients had molecularly confirmed ESBL-producers (of 117 *Enterobacteriaceae* characterised 71% were positive for at least a CTX-M-14 or CTX-M-15 enzyme). For *E. coli* and *K. pneumoniae* eradication rates were lower for ESBL-producing isolates, with evidence of fluoroquinolone co-resistance phenomena.

Table 34

Table 27: Per-Pathogen Microbiologic Eradication Rates (Outcomes) at the TOC Visit (ME at TOC Population)

Baseline Pathogen Category Organism Group/ Pathogen Response	Ceftolozane/ Tazobactam (N=340) n (%)	Levofloxacin (N=353) n (%)	% Difference (95% CI)
Gram-Negative Aerobes			
Gram-Negative Aerobes	N1=322	N1=340	
Eradication	282 (87.6)	255 (75.0)	12.6 (6.67, 18.38)
Persistence	40 (12.4)	85 (25.0)	
Enterobacteriaceae	N1=315	N1=327	
Eradication	276 (87.6)	248 (75.8)	11.8 (5.82, 17.64)[a]
Persistence	39 (12.4)	79 (24.2)	
Escherichia coli	N1=261	N1=284	
Eradication	232 (88.9)	219 (77.1)	11.8 (5.49, 17.94)[a]
Persistence	29 (11.1)	65 (22.9)	
Escherichia coli (ESBL-Producing)	N1=36	N1=36	
Eradication	26 (72.2)	17 (47.2)	Not available
Persistence	10 (27.8)	19 (52.8)	
Escherichia coli (CTX-M-14/15)[b]	N1=27	N1=25	
Eradication	19 (70.4)	13 (52.0)	Not available
Persistence	8 (29.6)	12 (48.0)	
Klebsiella pneumoniae	N1=25	N1=23	
Eradication	21 (84.0)	14 (60.9)	23.1 (-2.09, 45.39)
Persistence	4 (16.0)	9 (39.1)	
Klebsiella pneumoniae (ESBL-Producing)	N1=10	N1=7	
Eradication	7 (70.0)	2 (28.6)	Not available
Persistence	3 (30.0)	5 (71.4)	
Klebsiella pneumoniae (CTX-M-14/15)[b,c]	N1=8	N1=4	
Eradication	5 (62.5)	1 (25.0)	Not available
Persistence	3 (37.5)	3 (75.0)	
Proteus mirabilis	N1=10	N1=11	
Eradication	10 (100)	8 (72.7)	27.3 (-5.55, 56.56)
Persistence	0	3 (27.3)	
Pseudomonas aeruginosa	N1=7	N1=12	
Eradication	6 (85.7)	6 (50.0)	35.7 (-8.75, 62.98)
Persistence	1 (14.3)	6 (50.0)	
Enterobacter cloacae	N1=6	N1=7	
Eradication	2 (33.3)	6 (85.7)	-52.4 (-78.78, -0.27)
Persistence	4 (66.7)	1 (14.3)	
Gram-Positive Aerobes			
Gram-Positive Aerobes	N1=21	N1=20	
Eradication	7 (33.3)	16 (80.0)	-46.7 (-66.74, -16.33)
Persistence	14 (66.7)	4 (20.0)	
Enterococcus faecalis	N1=16	N1=16	
Eradication	5 (31.3)	12 (75.0)	-43.8 (-66.37, -9.21)
Persistence	11 (68.8)	4 (25.0)	
Enterococcus faecium	N1=2	N1=3	
Eradication	1 (50.0)	3 (100)	-50.0 (-90.55, 19.26)
Persistence	1 (50.0)	0	

Superinfections were observed on 3.8% ceftolozane/tazobactam and 5.7% levofloxacin patients and new infections occurred in 8.8% and 6.5%. Enterococci predominated in these patients.

Ancillary analyses

The subgroup analyses showed some important findings, several of which were influenced by the interplay between factors linked to the baseline diagnosis and the predominance of patients with pyelonephritis. Hence interpretation of the subgroup findings must take into account the differences in

gender, age and CrCL between the pyelonephritis and cUTI groups. The apparent geographical differences may also be linked to the type of patient mostly enrolled at some sites.

Due to the rates of baseline fluoroquinolone resistance it is important to note the outcomes for the subsets with levofloxacin-susceptible or resistant pathogens at baseline. Among the levofloxacin-resistant pathogens inevitably ceftolozane-tazobactam did better but the responses were much lower than for the levofloxacin-susceptible patients. This apparent difference reflected the summation of predominance of cUTI patients with levofloxacin-resistant pathogens and co-resistance between FQ-R determinants and expression of beta-lactamases that hydrolysed ceftolozane despite the presence of tazobactam.

Table 35

Ta robiological Response at TOC Visit by Overall Population and groups (ME at TOC Population) (Continued)

Subgroup/Population Microbiological Response	Ceftolozane/Tazobactam n (%)	Levofloxacin n (%)	% Difference (95% CI)
Region			
Eastern Europe[d]	N=269	N=275	
Success	228 (84.8)	208 (75.6)	9.1 (2.42, 15.73)
Failure	41 (15.2)	67 (24.4)	
North America	N=10	N=7	
Success	7 (70.0)	6 (85.7)	-15.7 (-48.22, 26.00)
Failure	3 (30.0)	1 (14.3)	
South America	N=25	N=34	
Success	23 (92.0)	23 (67.6)	24.4 (2.84, 42.12)
Failure	2 (8.0)	11 (32.4)	
Rest of World	N=36	N=37	
Success	30 (83.3)	29 (78.4)	5.0 (-13.39, 22.84)
Failure	6 (16.7)	8 (21.6)	
Age Categories 1			
≥18 to <65	N=260	N=266	
Success	222 (85.4)	212 (79.7)	5.7 (-0.83, 12.15)
Failure	38 (14.6)	54 (20.3)	
≥65 to <75	N=45	N=44	
Success	38 (84.4)	27 (61.4)	23.1 (4.59, 39.76)
Failure	7 (15.6)	17 (38.6)	
≥75	N=35	N=43	
Success	28 (80.0)	27 (62.8)	17.2 (-3.22, 35.16)
Failure	7 (20.0)	16 (37.2)	

Table 36

Microbiological Response at TOC Visit by Overall Population and Subgroups (ME at TOC Population)

Subgroup/Population Microbiological Response	Ceftolozane/Tazobactam n (%)	Levofloxacin n (%)	% Difference (95% CI)
Overall Population (Primary Analysis - ME at TOC)			
Overall Analysis	N=340	N=353	
Success	288 (84.7)	266 (75.4)	9.4 (1.54, 17.12)[a]
Failure	52 (15.3)	87 (24.6)	
Diagnosis			
Pyelonephritis	N=280	N=287	
Success	242 (86.4)	231 (80.5)	5.9 (-0.20, 12.04)
Failure	38 (13.6)	56 (19.5)	
cLUTI	N=60	N=66	
Success	46 (76.7)	35 (53.0)	23.6 (6.91, 38.47)
Failure	14 (23.3)	31 (47.0)	
Subjects with Levofloxacin-Resistant Baseline Uropathogens[b]			
Levofloxacin-Resistant	N=89	N=99	
Success	58 (65.2)	42 (42.4)	22.7 (8.47, 35.73)
Failure	31 (34.8)	57 (57.6)	
Subjects with Levofloxacin-Susceptible Baseline Uropathogens			
Levofloxacin-Susceptible	N=232	N=228	
Success	216 (93.1)	201 (88.2)	4.9 (-0.4, 10.4)
Failure	16 (6.9)	27 (11.8)	
Creatinine Clearance[c]			
<50 mL/min	N=25	N=26	
Success	20 (80.0)	17 (65.4)	14.6 (-9.82, 36.78)
Failure	5 (20.0)	9 (34.6)	
≥50 mL/min	N=314	N=327	
Success	268 (85.4)	249 (76.1)	9.2 (3.10, 15.22)
Failure	46 (14.6)	78 (23.9)	
Bacteraemia at Baseline			
Yes	N=24	N=26	
Success	21 (87.5)	20 (76.9)	10.6 (-11.50, 31.23)
Failure	3 (12.5)	6 (23.1)	
No	N=316	N=327	
Success	267 (84.5)	246 (75.2)	9.3 (3.06, 15.37)
Failure	49 (15.5)	81 (24.8)	

There were 24 ME patients with bacteraemia treated with ceftolozane/tazobactam and 23/24 had pyelonephritis. The single patient with cLUTI was infected with *K. oxytoca* susceptible to both study drugs and achieved microbiological and clinical success. The 23 patients with pyelonephritis had monomicrobial infections including 20 with *E. coli* (2 of which were confirmed ESBL producers) and single patients with each of *K. pneumoniae*, *P. mirabilis* and *E. aerogenes* (also ESBL-positive). Twenty of 23 (87%) patients achieved microbiological success at TOC. The 3 failures had *E. coli*, one of which was ESBL positive. Clinical success was reported for 22/23 and the single failure was infected with an ESBL-negative *E. coli*.

There were 241 patients in the ME population (127 [37.4%] ceftolozane-tazobactam vs. 114 [32.3%] levofloxacin) with renal impairment at baseline, most of whom had mild renal impairment. Dosing adjustments were required when CLCR was ≤ 50 mL/min and 23/51 patients received appropriate adjusted doses at baseline.

The microbiological outcomes for renally impaired patients compared very closely to those for the general population. In the ceftolozane-tazobactam group the microbiological outcomes for the subsets with moderate or severe renal impairment, with and without appropriate dose adjustment at baseline, were only slightly lower compared to those with normal renal function.

For the 567 patients with pyelonephritis in the ME population, the eradication rates were generally consistent with the primary analysis as far as can be discerned based on some small denominators.

CXA-cIAI-10-08-09: A Multicentre, Double-blind, Randomised, Phase 3 Study to Compare the Efficacy and Safety of Intravenous Ceftolozane/Tazobactam with that of Meropenem in Complicated Intra-abdominal Infections

Methods

Study Participants

Eligible adults had to meet all of the following inclusion criteria:

- Had 1 of the following diagnoses (with evidence of intraperitoneal infection):
  a. Cholecystitis (including gangrenous) with rupture, perforation, or progression of the infection beyond the gallbladder wall;
  b. Diverticular disease with perforation or abscess;
  c. Appendiceal perforation or peri-appendiceal abscess (limited to 30% in protocol);
  d. Acute gastric or duodenal perforation, only if operated on >24 hours after perforation occurred;
  e. Traumatic perforation of the intestine, only if operated on >12 hours after perforation occurred;
  f. Peritonitis due to other perforated viscus or following a prior operative procedure;
  g. Subjects with inflammatory bowel disease or ischaemic bowel disease were eligible provided there was bowel perforation.
  h. Intra-abdominal abscess (including liver or spleen);
- Required surgical intervention within 24 hours of (before or after) the first dose of study drug
- If failed prior antibacterial treatment for the current cIAI, must have a positive culture from an intra-abdominal site and require surgical intervention
- Evidence of systemic infection including one or more of the following was also required:
  a. Temperature (oral) greater than 38°Celsius (C) or less than 35°C;
  b. Elevated white blood cells (WBC; >10 500/mm3);
  c. Abdominal pain, flank pain, or pain likely due to cIAI that is referred to another anatomic area such as back or hip; or
  d. Nausea or vomiting.

Pre-operative enrolment and dosing was acceptable, provided that the sample from the site of infection is obtained during the interventional procedure.

Treatments

Patients received (1:1) ceftolozane/tazobactam 1.5 g q8h plus metronidazole 500 mg q8h as consecutive 1-h infusions or meropenem 1 g q8h as 1-h infusions for 4-10 days (max 14 days).

Objectives

The primary objective was to demonstrate non-inferiority for ceftolozane/tazobactam vs. meropenem based on cure rates at TOC; 26 to 30 days from randomisation) in the CE population using a margin of 12.5% at a 1-sided 0.005 significance level. The analysis in the ITT population was secondary.

Outcomes/endpoints

An EOT visit occurred within 24 h after the last dose of study drug. The TOC was 26 to 30 days after the first dose of study drug and the LFU visit at 38 to 45 days after the first dose of study drug.

Definitions of clinical outcomes:

Clinical Cure (EOT, TOC): Complete resolution or significant improvement in signs and symptoms such that no antibacterial therapy or surgical or drainage procedure was required for the index infection

Clinical Failure: Death related to IAI, persisting or recurrent infection requiring additional intervention, need for additional antibacterial therapy or surgical wound infection

Indeterminate (TOC, LFU): Study data were not available for evaluation of efficacy for any reason

Sustained clinical cure (at LFU): no signs or symptoms recur or worsen since TOC

Relapse: Signs, symptoms and/or radiographic findings of IAI (including wound infection) recur or worsen since the TOC

Microbiological response

Site of infection sample for culture was obtained at screening and further samples if clinically indicated. Samples were analysed in a central laboratory. The usual definitions were applied. For an overall microbiological response of success all baseline pathogen were to be eradicated.

Sample size

Randomisation (1:1) of 494 per treatment arm across the two studies (CXA-cIAI-10-08 and CXA-cIAI-10-09) was expected to provide 370 CE patients per treatment, which would provide an overall power of ~ 99% in terms of the primary hypothesis assuming an evaluability rate of 75% and cure rate of 86.6%.

Randomisation

Randomisation (1:1) used IVRS/IWRS. Block randomisation was used, stratified by investigational site. There was stratification by primary site of infection with 2 levels: bowel (small or large) vs. other sites

Blinding (masking)

The study were double-blind. An unblinded study site pharmacist or designee prepared and administered the study drug infusions.

Statistical methods

Study populations were defined as follows:

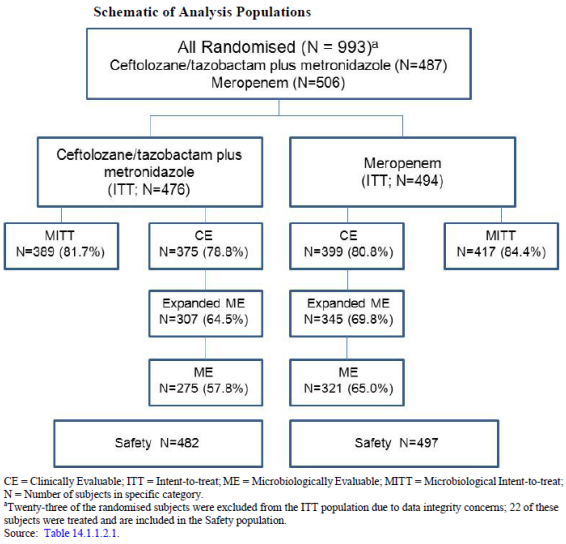
- ITT and Safety – as above
- MITT - all randomised with a pathogen isolated from an appropriate baseline specimen
- CE - all randomised who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study protocol and had a TOC visit within the window
- ME - all CE with a pathogen susceptible to the study drug
- Expanded ME - all in the MITT population who met all CE criteria.

Results

Participant flow

Patient disposition is shown in the figure. There were 23 subjects from 2 study sites excluded from the ITT population due to concerns regarding integrity of data. The imbalance in the proportions eligible for the ME population reflected higher numbers in the ceftolozane/tazobactam group without a baseline pathogen, with a non-susceptible pathogen or without a clinical outcome at TOC.

Figure 14



CE = Clinically Evaluable; ITT = Intent-to-treat; ME = Microbiologically Evaluable; MITT = Microbiological Intent-to-treat; N = Number of subjects in specific category.
[a]Twenty-three of the randomised subjects were excluded from the ITT population due to data integrity concerns; 22 of these subjects were treated and are included in the Safety population.
Source: Table 14.1.1.2.1.

Recruitment

Patients were enrolled at 128 sites with ~80% enrolled in Europe and 10.5% in S. America.

Conduct of the study

After first enrolment CXAcIAI-10-08 and CXA-cIAI-10-09 were combined with a plan to enrol ~500 per protocol and a change in the level of significance (Protocol version 3.2 10 April 2013). The primary analysis was changed to the CE population. There was no significant treatment-by-protocol interaction in either population.

Baseline data

Baseline demographics were generally balanced between treatment groups. Despite the protocol limit infections originating from the appendix predominated (48% in the CE population). The mean age was 50.7 years and only 23% were aged > 65 years. Less than one third had renal impairment and > 80% had an APACHE II score <10 (median 5).

Table 37

Table 16: Anatomic Site of Infection, Primary Diagnosis, Disease Characteristics and Surgical Intervention (ITT Population)

Characteristic	Ceftolozane/ Tazobactam + Metronidazole (N = 476) n (%)	Meropenem (N = 494) n (%)	Total (N = 970) n (%)
Primary Site of Infection			
Bowel (small or large)	85 (17.9)	88 (17.8)	173 (17.8)
Other Site of IAI	391 (82.1)	404 (81.8)	795 (82.0)
Missing	0	2 (0.4)	2 (0.2)
Anatomic Site of Origin of Current Infection[a]			
Stomach/Duodenum	61 (12.8)	55 (11.1)	116 (12.0)
Biliary - Cholecystitis	91 (19.1)	96 (19.4)	187 (19.3)
Biliary - Cholangitis	2 (0.4)	1 (0.2)	3 (0.3)
Small Bowel	28 (5.9)	21 (4.3)	49 (5.1)
Appendix	209 (43.9)	219 (44.3)	428 (44.1)
Colon	59 (12.4)	70 (14.2)	129 (13.3)
Parenchymal (liver)	19 (4.0)	22 (4.5)	41 (4.2)
Parenchymal (spleen)	4 (0.8)	3 (0.6)	7 (0.7)
Other	11 (2.3)	13 (2.6)	24 (2.5)

Outcomes and estimation

The primary analysis demonstrated non-inferiority. The actual cure rates were very high in both treatment groups. Results for the ITT population and sensitivity analyses were consistent with the primary analysis.

Table 38

Ta mary and Secondary Analysis for Noninferiority of Clinical Response he Test-of-Cure Visit (CE and ITT Populations)

Analysis	Clinical Response	Ceftolozane/ Tazobactam + Metronidazole n (%)	Meropenem n (%)	Percentage Difference[a] (99% CI)
Primary Analysis[b]		N = 375	N = 399	
CE Population	Cure	353 (94.1)	375 (94.0)	0.0 (-4.16, 4.30)
	Failure	22 (5.9)	24 (6.0)	
Secondary Analysis[c]		N = 476	N = 494	
ITT Population	Cure	399 (83.8)	424 (85.8)	-2.2 (-7.95, 3.44)
	Failure	77 (16.2)	70 (14.2)	
	Observed failure	35 (7.4)	36 (7.3)	
	Indeterminate imputed as failure	42 (8.8)	34 (6.9)	

In the ITT population (counting observed failures and default failures) failures in the ceftolozane/tazobactam group were more likely to be elderly subjects (44.2% vs. 27.1%), have peritonitis (76.6% vs. 64.3%) and have had a laparotomy (64.9% vs. 48.6%) compared to meropenem-treated failures. For CE patients with bacteraemia clinical (and microbiological) failure was seen in 2/8 (25%) in the ceftolozane/tazobactam and in 1/13 (7.7%) in the meropenem group.

The majority of microbiological assessments were presumed (only 27 patients had a documented microbiological outcome) and therefore largely reflected clinical responses.

- For the 58 ESBL-positive pathogens in the MITT dataset the clinical cure rates were 25/29 (86.2%) for ceftolozane-tazobactam vs. 24/29 (82.8%) for meropenem. Cure rates for *E. coli* with CTX-M-14 or CTX-M-15 ESBLs were 9/11 (81.8%) and 8/11 (72.7%), respectively.
- In the MITT population 68/69 *P. aeruginosa* were susceptible to ceftolozane/tazobactam and 62/69 susceptible to meropenem. Overall cure rates were 30/38 (79%) vs. 30/34 (88%). Of 52 *P. aeruginosa* isolates tested, 8 (15.4%) over-expressed AmpC and had ceftolozane/tazobactam

MICs in the range 0.5-16 µg/mL, of which 7 had MICs ≤ 8 µg/mL. Five of the 8 were treated with ceftolozane/tazobactam and 4 were cured.

Table 39

Summary and Analysis of Per-Pathogen Microbiological Eradication of Baseline Intra-abdominal Pathogens at the Test-of-Cure Visit (ME Population) for Pathogens Isolated in ≥10 Subjects in the Ceftolozane/tazobactam Plus Metronidazole Treatment Arm

Intra-abdominal Pathogen Category Intra-abdominal Pathogen	Ceftolozane/tazobactam + Metronidazole N = 275 n (%)	Meropenem N = 321 n (%)	Percentage Difference in Eradication[a] Rate (95% CI)[b]
Gram-Negative Aerobes	N1 = 243	N1 = 282	
	234 (96.3)	269 (95.4)	0.9 (-2.80, 4.48)
Enterobacteriaceae	232	266	
	223 (96.1)	253 (95.1)	1.0 (-2.88, 4.77)
Enterobacter cloacae	21	22	
	18 (85.7)	22 (100)	-14.3 (-34.64, 3.25)
Escherichia coli	201	225	
	193 (96.0)	214 (95.1)	0.9 (-3.34, 5.05)
Klebsiella oxytoca	12	22	
	12 (100)	21 (95.5)	4.5 (-19.99, 21.80)
Klebsiella pneumoniae	28	25	
	28 (100)	22 (88.0)	12.0 (-2.38, 29.96)
Proteus mirabilis	11	10	
	10 (90.9)	9 (90.0)	0.9 (-28.89, 32.23)
Pseudomonas aeruginosa	25	28	
	25 (100)	28 (100)	0.0 (-13.32, 12.06)

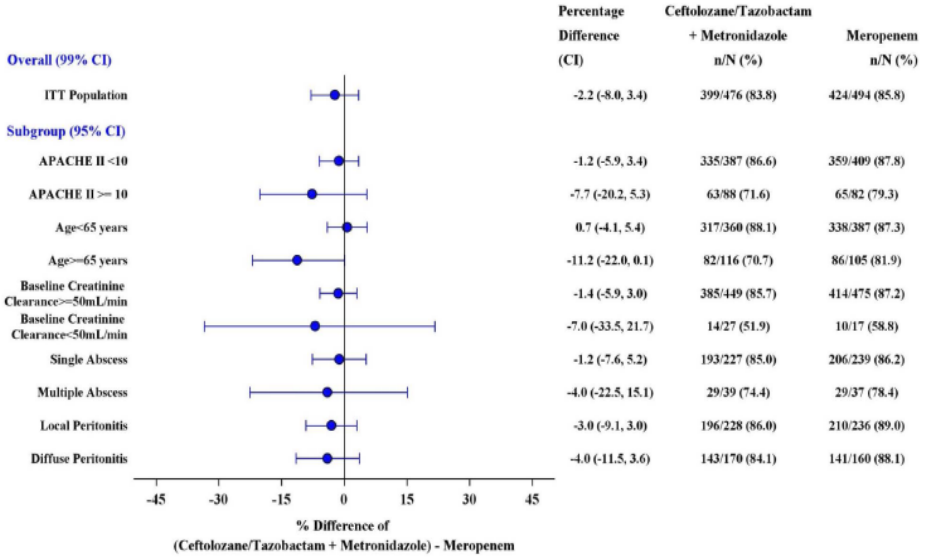
Approximately 75% of patients were clinically evaluable at LFU and none had a relapse. Superinfections were seen in 10/389 (2.6%) vs. 13/417 (3.1%) in the ceftolozane/tazobactam and meropenem groups, respectively, while 12/389 (3.1%) vs. 9/417 (2.2%) had new infections. There was no consistent pattern for superinfecting pathogens (26 species) or new infection pathogens (27 species), although *E. faecium* and *E. faecalis* accounted for 6 vs. 5 superinfections and 6 vs. 4 new infections per group. No emergence of decreased susceptibility or resistance was observed.

Ancillary analyses

The sub-group analyses mostly showed point estimates that favoured meropenem. The difference was more marked in the ITT population, which the applicant ascribed to higher rates of indeterminate outcomes in the ceftolozane/tazobactam group. This difference reflected several factors but was mainly driven by premature discontinuations of study drug due to AEs and patient withdrawals.

Figure 15

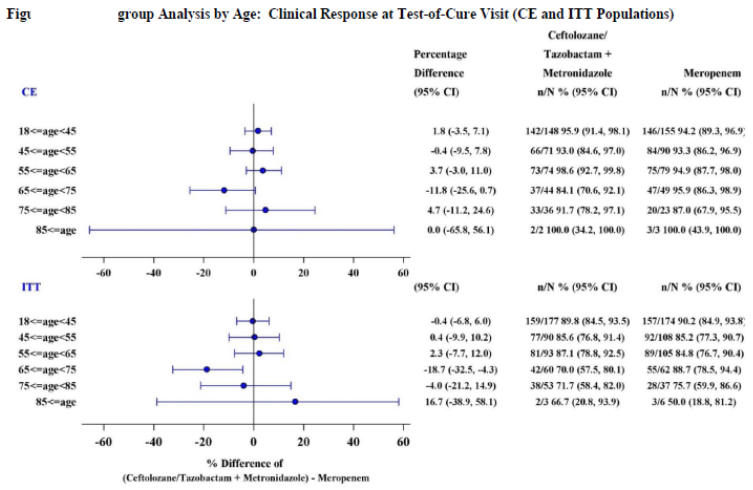
Figure 5: Subgroup Analysis by Selected Baseline Characteristics: Clinical Response at Test-of-Cure Visit (ITT Population)



There were no significant differences between treatment groups for cure rates in the CE and ITT populations by primary site of infection but there were differences in cure rates for each treatment according to the primary site. For example, cure rates for appendiceal infections were 96.6% vs. 96.4% in the CE and 89% vs. 91.8% in the ITT populations but cure rates for colonic primary sites were 84.2% vs. 87.5% and 66.1% vs. 71.4% in respective populations.

Older patients (> 65 – 75 years) had lower clinical response rates in both the CE and ITT population with ceftolozane/tazobactam than with meropenem. In this group, the primary site of infection was more frequently the bowel. No significant difference was observed in patients < 65 or > 75 years of age.

Figure 16



Clinical response rates were lower in North America (approximately 69%) than in Eastern Europe (approximately 89%) for both study treatments. The majority was enrolled in E. Europe but the proportion with appendicitis (41%) was about the same as that in N. America (44%) and pooled other countries (40%). Also, similar proportions were aged < 65 years in E. Europe vs. pooled other countries.

Summary of main studies

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 40. Summary of efficacy for trial CXA-cUTI-10-04 and CXA-cUTI-10-05

Title: A Multicentre, Double-Blind, Randomised, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam and Intravenous Levofloxacin in Complicated Urinary Tract Infection, Including Pyelonephritis			
Study identifier	Protocol Number: CXA-cUTI-10-04 and CXA-cUTI-10-05 EudraCT Number: 2010-023452-87 (-04); 2010-023452-11 (-05) ClinicalTrials.gov identifiers: NCT01345929 (-04) and NCT01345955 (-05)		
Design	Multicentre, prospective, randomised, double-blind, double-dummy Phase 3 study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Day 1 to Day 42 including treatment phase, End-of-Therapy (EOT) visit, Test-of-Cure (TOC) visit, and Late follow-up (LFU) visit. Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	ceftolozane/tazobactam		Ceftolozane/tazobactam 1.5 g every 8 hours, 543 subjects randomized
	levofloxacin		Levofloxacin 750 mg once daily, 540 subjects randomized
Endpoints and definitions	Primary endpoint	Microbiological response rate in the ME population at the TOC visit	Demonstrate the noninferiority of ceftolozane/tazobactam versus comparator (levofloxacin) based on the difference in microbiological response rate in the ME population at the TOC visit (ceftolozane/tazobactam minus comparator [levofloxacin]) using a noninferiority margin of 10%, at a 1-sided 0.005 significance level.
	Key secondary endpoint	Microbiological response rate in the mMITT population at the TOC visit	Demonstrate the noninferiority of ceftolozane/tazobactam versus comparator (levofloxacin) based on the difference in microbiological response rate in the mMITT population at the TOC visit (ceftolozane/tazobactam minus comparator [levofloxacin]), using a noninferiority margin of 10%, at a 1-sided 0.005 significance level.
Database lock	08 November 2013		

Results and Analysis			
Analysis description	**Primary Analysis - Microbiological response rate in the ME population at the TOC visit**		
Analysis population and time point description	Microbiologically Evaluable at Test-of-Cure (ME at TOC): A subset of the CE at TOC population who adhered to study procedures and had an appropriately collected urine culture specimen and interpretable urine culture result at the TOC visit. Test-of-Cure (TOC) visit analysis window (7 days [± 2 days] after last treatment)		
Descriptive statistics and estimate variability	Treatment group	Ceftolozane/ Tazobactam	Levofloxacin
	Number of subject	340	353
	Success [n, (%)]	288 (84.7)	266 (75.4)
	Failure [n, (%)]	52 (15.3)	87 (24.6)
Effect estimate per comparison	Percentage Difference (99% CI)	9.4 (1.54, 17.12)	
Analysis description	**Key Secondary analysis - Microbiological response rate in the mMITT population at the TOC visit**		
Analysis population and time point description	Microbiological Modified Intent-to-Treat (mMITT): A subset of the MITT that included subjects who had at least 1 qualified uropathogen from a study-qualifying pretreatment baseline urine specimen. TOC visit analysis window (7 days [± 2 days] after last treatment)		
Descriptive statistics and estimate variability	Treatment group	Ceftolozane/ Tazobactam	Levofloxacin
	Number of subject	398	402
	Success [n, (%)]	313 (78.6)	281 (69.9)
	Failure [n, (%)]	85 (21.4)	121 (30.1)
	Observed Failure [n, (%)]	57 (14.3)	94 (23.4)
	Non-evaluable [n, (%)]	28 (7.0)	27 (6.7)
Effect estimate per comparison	Percentage Difference (99% CI)	8.7 (0.77, 16.57)	
Notes	In addition to demonstrating the noninferiority of ceftolozane/tazobactam to levofloxacin, the lower bound of the 2-sided 99% CI exceeded zero in both the primary and key secondary analysis populations, indicating superiority of ceftolozane/tazobactam over levofloxacin.		

Table 41. Summary of efficacy for trial CXA-cIAI-10-08 and CXA-cIAI-10-09

Title: A Multicentre, Double-blind, Randomised, Phase 3 Study to Compare the Efficacy and Safety of Intravenous Ceftolozane/Tazobactam with that of Meropenem in Complicated Intra-abdominal Infections				
Study identifier	Protocol Number: CXA-cIAI-10-08 and CXA-cIAI-10-09 EudraCT number: 2011-002119-27 (-08); 2011-002120-41 (-09)			
Design	Multicentre, prospective, randomised, double-blind, Phase 3 study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Day 1 to Day 45 including treatment phase, End-of-Therapy (EOT) visit, Test-of-Cure (TOC) visit, and Late follow-up (LFU) visit. Not applicable Not applicable	
Hypothesis	Noninferiority			
Treatments groups	ceftolozane/tazobactam +metronidazole		Ceftolozane/tazobactam 1.5 g every 8 hours plus metronidazole 500 mg every 8 hours 487 subjects randomised	
	meropenem		Meropenem 1000 mg every 8 hours and a matching saline placebo 506 subjects randomised	
Endpoints and definitions	Primary endpoint	Clinical cure rate (CE)	Clinical cure rate in the CE population at the TOC visit based on the difference in clinical cure rates (ceftolozane/tazobactam minus meropenem) using a noninferiority margin of 12.5%, at a 1-sided 0.005 significance level.	
	Key secondary endpoint	Clinical cure rate (ITT)	Clinical cure rate in the ITT population at the TOC visit based on the difference in clinical cure rates (ceftolozane/tazobactam minus meropenem) using a noninferiority margin of 12.5%, at a 1-sided 0.005 significance level.	
Database lock	27 November 2013			
Results and Analysis				
Analysis description	**Primary Analysis - Clinical cure rate (CE)**			
Analysis population and time point description	Clinically Evaluable (CE): The CE population was a subset of the ITT population of subjects who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a TOC visit within the specified visit window. Test-of-Cure (TOC) visit analysis window (24 to 32 days after the initiation of study drug administration)			
Descriptive statistics and estimate variability	Treatment group		Ceftolozane/ Tazobactam + Metronidazole	Meropenem
	Number of subject		375	399
	Cure [n (%)]		353 (94.1)	375 (94.0)

	Failure [n, (%)]	22 (5.9)	24 (6.0)
Effect estimate per comparison	Percentage Difference (99% CI)	0.0 (-4.16, 4.30)	
Analysis description	**Key Secondary analysis - Clinical cure rate (ITT)**		
Analysis population and time point description	Intent-to-Treat (ITT): The ITT population consisted of all randomised subjects regardless of whether or not the subjects went on to receive study drug. Subjects in the ITT population were categorised based on the treatment that the subjects were randomised to, irrespective of what they actually received. Test-of-Cure (TOC) visit analysis window (24 to 32 days after the initiation of study drug administration)		
Descriptive statistics and estimate variability	Treatment group	Ceftolozane/ Tazobactam + Metronidazole	Meropenem
	Number of subject	476	494
	Cure [n (%)]	399 (83.8)	424 (85.8)
	Failure [n, (%)]	77 (16.2)	70 (14.2)
	Observed failure [n, (%)]	35 (7.4)	36 (7.3)
	Indeterminate imputed as failure [n, (%)]	42 (8.8)	34 (6.9)
Effect estimate per comparison	Percentage Difference (99% CI)	-2.2 (-7.95, 3.44)	
Notes	Twenty-three of the randomised subjects (11 in the ceftolozane/tazobactam + metronidazole arm and 12 in the meropenem arm) were excluded from the ITT population due to data integrity concerns.		

Table 42. Clinical studies in special populations (Safety Population)

	Trials	Age 65-74		Age 75-84		Age 85+		Total Age 65+	
		C/T	CMP	C/T	CMP	C/T	CMP	C/T	CMP
Controlled Trials	CXA-cUTI-10-04/05	77/533	80/535	48/533	51/535	9/533	9/535	134/533	140/535
	CXA-cIAI-10-08/09	60/482	62/497	53/482	36/497	3/482	6/497	116/482	104/497
	Pooled	137/ 1015	142/ 1032	101/ 1015	87/ 1032	12/ 1015	15/ 1032	250/ 1015	244/ 1032
Non Controlled Trials		NA		NA		NA		NA	

Notes:

All data presented as N/n (Older subjects number/total number)
No special studies were conducted in elderly subjects only
NA: Not applicable; C/T: Ceftolozane/Tazobactam; CMP: Comparator [cUTI, Levofloxacin; cIAI, Meropenem]

2.5.3. Discussion on clinical efficacy

Overall, the choice of the dosage regimen for the Phase 3 studies is based on pharmacokinetic and pharmacodynamic considerations as well as tolerability. No formal dose-finding study has been performed and the same dose of ceftolozane/tazobactam (1.5 g every 8 hours) is used in both of the applied indications.

Design and conduct of clinical studies

The Marketing Authorisation application rests on two single pivotal studies that generally comply with CHMP guidance regarding patient selection criteria, analyses populations and non-inferiority margins but do not comply with recommendations regarding the types of infections to be treated or, at least, the proportions of specific types of infections that could support the indications sought of cUTI and cIAI.

The choice of the dosage regimen for the Phase 3 studies is based on pharmacokinetic and pharmacodynamic considerations as well as tolerability. No formal dose-finding study has been performed and the same dose of ceftolozane/tazobactam (1.5 g every 8 hours) is used in both of the applied indications. However, it is questioned whether the performed PK/PD studies are sufficient in order to conclude on the optimal dose.

cUTI

The efficacy of ceftolozane/tazobactam in complicated urinary tract infections (cUTI) was evaluated in one pooled, multicentre, prospective, randomised, double-blind, double-dummy, Phase 3 study that enrolled 1083 patients.

The primary objective was to demonstrate non-inferiority of ceftolozane/tazobactam versus levofloxacin in adult subjects with cUTI, including pyelonephritis based on the difference in microbiological response rate in the microbiologically evaluable (n=693) population at the Test-of-Cure (TOC) visit.

Patients were randomly assigned to receive in a 1:1 ratio either ceftolozane/tazobactam IV (1.5 g every 8 hours) or levofloxacin IV (750 mg every 8 hours) and a matching saline IV placebo infusion for 7 days.

Levofloxacin was selected as the comparator and the applicant justifies this choice by stating that it is the most widely used agent for treatment of cUTI worldwide. The dose of levofloxacin used was higher than that recommended in the EU SmPC. However, based on the CLSI breakpoint, 30% of Gram-negative pathogens and 57% of Gram-positive pathogens were resistant to levofloxacin. This biased the overall results in favour of ceftolozane/tazobactam and demonstrated that levofloxacin was not a good choice of comparator for the selected study sites.

In general, the inclusion and exclusion criteria in the pivotal study are acceptable. There was one specific inclusion criterion stating that all patients included required IV antibacterial therapy for the treatment of the presumed cUTI indicating that the infections should be severe. However, an evaluation of severity of the infection and the symptoms (according to e.g. systemic laboratory diagnostic factors [i.e. CRP, leucocytes], presence of urosepsis) was lacking.

For the cLUTI diagnosis, there were differences between the treatment arms especially regarding the reasons for complications but also in the numbers of complicating factors. In the levofloxacin arm, fewer patients had 2 or more complicating factors such as indwelling catheter (7.6% vs. 13.3% in the ceftolozane/tazobactam arm), or were males with documented urinary retention (36.4% vs. 53.3% in the ceftolozane/tazobactam arm).

The demographic and baseline characteristics were similar between the 2 treatment arms. Most of the patients were white, females with a mean age of 48 years of age and recruited from Eastern Europe. A minority were elderly; approximately 24% were 65 years of age or older.

The total proportion of subjects randomised with acute pyelonephritis was approximately 80%, and stratification at enrolment according to diagnosis was not performed (studies predated current CHMP guideline). The most commonly isolated pathogen was as expected in this indication, *E.coli* 545/693 (78.6%), of which, 188/693 (27.1%) subjects had levofloxacin-resistant baseline uropathogens; 89 subjects in the ceftolozane/tazobactam treatment arm and 99 in the levofloxacin treatment arm, while 54/693 (7.8%) subjects had baseline uropathogens resistant to ceftolozane/tazobactam; 27 subjects in each treatment arm in the ME at TOC population.

The incidence of subjects with bacteraemia at baseline was 7.2% in the ME at TOC population and was balanced across the 2 treatment arms. The most common blood pathogen isolated at baseline was *E.coli*:16/24 (4.7%) pathogens in the ceftolozane/tazobactame treatment arm and 16/26 (4.5%) in the levofloxacin treatment arm.

Small number of pathogens were confirmed to be: ESBL-positive, or to be *E. coli* with CTX-M-14/CTX-M-15 ESBLs or *P. aeruginosa* overexpressing AmpC. Ceftolozane/tazobactam demonstrated activity against these resistant pathogens, however, no firm conclusions of the efficacy of ceftolozane/tazobactam towards these pathogens can be made due to limited numbers.

cIAI

The efficacy of ceftolozane/tazobactam in complicated intra-abdominal infection (cIAI) was evaluated in one pooled, multicentre, prospective, randomised, double-blind, placebo-dummy, Phase 3 study that included 993 patients.

The study aimed to demonstrate non-inferiority of ceftolozane/tazobactam plus metronidazole versus meropenem in adult subjects with cIAI based on the difference in clinical cure rates at the Test-of-Cure (TOC) visit in the Clinically Evaluable (CE) population (ceftolozane/tazobactam minus meropenem).

Patients were randomly assigned to receive in a 1:1 ratio either ceftolozane/tazobactam IV (1.5 g every 8 hours) plus metronidazole IV (500 mg every 8 hours) or meropenem IV (1 g every 8 hours) and a matching saline IV placebo infusion for 4-10 days (if study drug discontinuation criteria were not met by study day 10, the patients could receive treatment up to 14 days).

Meropenem was selected as the comparator. Meropenem is considered appropriate for the treatment of complicated IAIs, if the patients are severely ill (defined as, among other things, APACHE II scores > 15, advanced age, degree of peritoneal involvement/diffuse peritonitis, immunocompromised state, severe physiological disturbance). In general, severe intra-abdominal infections as seen in e.g. nosocomial infections where the risk of resistant pathogens is much higher compared to community-acquired infections, would justify the use of broad-spectrum carbapenems (like meropenem).

As most intra-abdominal infections are polymicrobial, involving both aerobic and anaerobic organisms, metronidazole was added to the ceftolozane/tazobactam arm with the intension of protecting against organisms not covered by ceftolozane/tazobactam. This is considered appropriate and in line with clinical recommendations.

The primary endpoint was the clinical cure rate in the CE population at the TOC visit. Key secondary endpoint was the clinical cure rate in the ITT population at the TOC visit. This is in accordance with the recommendations for cIAI set out in the current CHMP guidance (Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections; EMA/CHMP/351889/2013).

The inclusion criteria ensured that the intra-abdominal infections could be considered "complicated", as the required infections will lead to infectious processes proceeding beyond the organ that is the source of the infection. In general, the inclusion and exclusion criteria, including diagnoses and use of concomitant antibiotics, are in line with those used in previous studies on cIAI. Overall, the included types of intra-abdominal infections could be categorised as infections that are neither so limited that just surgery would be curative nor so complicated that several additional confounding factors would affect cure.

The treatment groups were generally well matched with respect to gender, age, ethnicity, race, BMI and disease characteristics. The majority of the enrolled subjects were male, white, had a normal renal function and were younger than 65 years (ITT population). Most subjects were recruited from Europe (in total 78.8%).

The severity of cIAI was classified using the APACHE II scoring system, in addition to assessment of the infectious process, signs of systemic infection and presence/absence of bacteraemia. Patients were analysed by APACHE II scores ≥ 10 and < 10. The chosen cut-off might have led to a relatively low enrolment of severely ill patients into the study.

E. coli, K. pneumoniae, P. aeruginosa and *P. mirabilis* were the most common aerobic, Gram-negative, baseline-infecting intra-abdominal pathogens isolated. Overall, this is as expected in these kinds of infections. Of the anaerobes, the Gram-negative anaerobes were most commonly isolated and of these *Bacteroides fragilis as most prominent*.

P. aeruginosa is generally more seldom detected in community-acquired cIAIs. Small numbers of pathogens were confirmed to be: ESBL-positive, or to be *E. coli* with CTX-M-14/CTX-M-15 ESBLs or *P. aeruginosa* overexpressing AmpC. Ceftolozane/tazobactam demonstrated activity against these resistant pathogens, however, no firm conclusions of the efficacy of ceftolozane/tazobactam plus metronidazole towards these pathogens can therefore be made due to limited numbers.

Efficacy data and additional analyses

cUTI

Non-inferiority of ceftolozane/tazobactam compared to levofloxacin was demonstrated both for the primary endpoint microbiological response rate in the ME at TOC population (84.7% in the ceftalozane/tazobactam arm vs. 75.4% in the levofloxacin arm) and for the key secondary endpoint

the microbiological response rate in the mMITT at TOC population (78.6% in the ceftalozane/tazobactam arm vs. 69.9% in the levofloxacin arm). The lower limits of both the 99% CIs were within -10 % (9.4 [1.54, 17.12] for the ME population and 8.7 [0.77, 16.57] for the mMITT population).

Non-inferiority was demonstrated for ceftolozane vs. levofloxacin in the subset with levofloxacin-susceptible pathogens as well as in a range of sensitivity analyses. Among the strains that were susceptible to levofloxacin, the microbiological success rates in the ME population at TOC were 93% for ceftolozane/tazobactam and 88% for levofloxacin. A *post hoc* evaluation indicated that 18% (96/567; 47 ceftolozane/tazobactam and 49 levofloxacin) of patients with pyelonephritis had a complicating factor. These patients with complicated pyelonephritis were generally older (mean age 57.8 years) and had a higher incidence of renal impairment (41.7%). There was a very high risk for microbial recurrence at the TOC visit explaining the lower microbiological eradication rates compared to the overall population with pyelonephritis (66.0% for ceftolozane/tazobactam vs. 65.3% for levofloxacin).

The study provides poor support for cLUTI, with only 60 vs. 66 ME patients with this diagnosis. In a sensitivity analysis of the primary endpoint limiting the population with cLUTI to patients with levofloxacin-susceptible pathogens the cure rate for ceftolozane/tazobactam in the ME population was 25/28 (89.3%) vs. 25/29 (86.2%) for levofloxacin (3.1% diff; 95% CI -15.37, 21.25).

cIAI

Non-inferiority of ceftolozane/tazobactam plus metronidazole compared to meropenem was demonstrated both for the primary endpoint clinical cure rate in CE at TOC (94.1% in the ceftalozane/tazobactam arm vs. 94% in the meropenem arm) and for the key secondary endpoint clinical cure rate in ITT at TOC (83.8% in the ceftalozane/tazobactam arm vs. 85.8% in the meropenem arm). The lower limits of both the 99% CIs were within -12.5% (0.0 [-4.16, 4.30] for the CE population and -2.2 [-7.95, 3.44] for the ITT population).

Results from the sensitivity analyses for the primary efficacy outcome and the key secondary efficacy outcome supported the results seen for the primary and the key secondary analyses, respectively.

Ceftolozane/tazobactam plus metronidazole showed significant and corresponding activity against the common IAI pathogens as evidenced by the high per-pathogen microbiological eradication rates. The results were comparable to the rate observed for the meropenem group (over 90% in both arms for all Gram-negative aerobes, Gram-negative anaerobes, Gram-positive aerobes and Gram-positive anaerobes). The most commonly isolated pathogen was *E. coli* and the eradication rate was 96% for ceftolozane/tazobactam plus metronidazole vs. 95.1% in the meropenem arm, with a 95% CI of 0.9 (-3.34, 5.05) in the microbiological evaluable (ME) population. The eradication rate, however, was lower for *Enterobacter cloacae* and *Streptococcus anginosus* for ceftolozane/tazobactam vs. meropenem. This indicates that these pathogens have lower susceptibility to ceftolozane/tazobactam (which was also reflected by the rather high MIC-values observed for ceftolozane/tazobactam for these specific microorganisms).

The per-subject microbiological success rate at TOC was high in the ME population (96% in the ceftolozane/tazobactam plus metronidazole arm vs. 95.6% in the meropenem arm with 95% CI of 0.4 [-3.13, 3.69]). These results were supported by the results achieved for the MITT population.

A high cure rate (> 95%) was observed in both treatment arms at EOT indicating a rapid initial effect of ceftolozane/tazobactam.

At LFU both study groups showed a high degree of durability of clinical effect with few relapses since the TOC visit (none for ceftolozane/tazobactam vs. 2 in the meropenem arm).

Clinical cure rates were comparable between the two treatment arms for subjects with a polymicrobial infection in the CE population and those with a monomicrobial infection in the CE and ITT populations. This result was not fully supported by the results achieved in the ITT population for the polymicrobial infections as the lower end of the 95% CI was below -12.5%.

About half of ITT and CE patients had a primary focus of infection in the appendix (compared to a maximum of 30% recommended in current CHMP guidance). In ITT and ME populations the cure rates were very high for infections of appendiceal origin (e.g. ITT 89% ceftolozane/tazobactam and 92% meropenem) and much lower for infections originating from the colon (e.g. ITT 66% vs. 71%).

Subgroup analyses seem to indicate that ceftolozane/tazobactam performs more poorly compared to meropenem in "high-risk" patients; more than 80% of patients in the study had an APACHE score <10 and that, especially in the ITT population, point estimate cure rates were numerically lower for ceftolozane/tazobactam vs. meropenem in those with APACHE scores > 10 (most of whom had non-appendiceal primary infection), in patients aged > 65 years (in whom the primary site of infection was more often the bowel) and in those with multiple abscess or diffuse peritonitis. Correlating with these findings the failures in the ceftolozane/tazobactam group were more likely to be elderly subjects (44.2% vs. 27.1% meropenem failures), have peritonitis (76.6% vs. 64.3%) and have had a laparotomy (64.9% vs. 48.6%). Cure rates were also lower in patients with moderate impairment of renal function compared to those with normal or mildly impaired renal function. However, this was observed in both treatment groups and the denominators were relatively small such that it is not possible to conclude that there was a real difference between treatments in this regard.

The applicant attempted to address these concerns based on the fact that outcomes were comparable between treatments in the CE population and that the imbalances that caused concern were due to higher rates of indeterminate outcomes in the ceftolozane/tazobactam group, which defaulted to failures in the ITT population analysis. Indeed, 42/76 ITT patients with an indeterminate clinical response were in the ceftolozane/tazobactam group. The difference reflected 23 vs. 16 with premature discontinuation of study drug for reasons that included AEs (2.1% vs. 0.8%), withdrawal (1.9% vs. 1.2%) and deaths unrelated to cIAI (1.5% vs. 1.0%).

Additional expert consultation

The CHMP consulted the Infectious Diseases Working Party (IDWP) on the suitability of the indications (Annex 8).

Reference was made to the Addendum to the core guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (Addendum to CPMP/EWP/558/95 Rev 2) which states:

"*If the range of infection types that has been studied within each indication is considered to be limited or was restricted to specific pathogens it might be considered necessary to further qualify the indication. In addition, a qualification of an indication may be needed if there is clear evidence that the test agent does not provide adequate efficacy in a specific and important subset of patients that would otherwise be assumed to be included under the indication.*

An alternative to qualification of the indication is to mention the limitations of the data only in section 4.4, with a cross-reference from section 4.1. For example, this may apply when very few cases of concomitant bacteraemia or very few cases of a particular type of infection have been treated within any one indication and when an indication for use has been based on very limited data."

It was clarified that the cited guideline passage considers the consequences of a limited dataset. This may refer to limitations in terms of the representation of a subset of patients defined by clinical syndrome, or a subset of the microorganisms that may cause the clinical syndrome.

In the case that the limitation resides in the number of patients represented in the subset, the crucial distinction between a restriction of indication and a mention of the limitation of data, is based on whether the totality of evidence, including PK/PD considerations, allow for an inference of positive B/R in the relevant subset of patients. Given that a positive benefit-risk (B/R) can be concluded, no restriction in the indication is mandated; however, the limitations to data may relate to the precision of the efficacy estimate, and to the relative efficacy versus the comparator/standard of care. In such cases, a cautionary statement of the lack of data, rather than a restriction of the indication, may be mandated for the consideration of the prescriber.

Further, it is not unusual that some of the pathogens that may cause the clinical syndrome for which the agent is indicated, are known to have limited or no susceptibility to the drug. It might also be unclear whether drug exposure at the proposed dose is sufficient in case of reduced susceptibility. In such situations, it may be preferable to describe considerations on microbial susceptibility in sections 4.4 and/or 5.1 rather than formally restricting the indication with respect to the microbial cause of the syndrome in question.

In drafting the guideline, careful consideration was given to situations in which a relevant subpopulation studied was so limited that section 4.1 might have to be restricted accordingly. However, it was not possible to provide specific recommendations given that this would depend on the available data. Specific recommendations are unlikely to be able to anticipate all potential situations. For example, if ceftolozane/tazobactam was not mainly excreted unchanged in the urine the efficacy shown for acute pyelonephritis could not be used to heavily support use in cUTI.

2.5.4. Conclusions on the clinical efficacy

For the overall ME population in study CXA-cUTI-10-04 /CXA-cUTI-10-05, 81.8% had pyelonephritis and non-inferiority was demonstrated for ceftolozane vs. levofloxacin in the subset with levofloxacin-susceptible pathogens as well as in a range of sensitivity analyses. A *post hoc* evaluation indicated that 18% (96/567; 47 ceftolozane/tazobactam and 49 levofloxacin) of patients with pyelonephritis had a complicating factor.

The study provides poor support for cUTI, with only a small number of ME patients with this diagnosis. Nevertheless, CHMP accepts that ceftolozane/tazobactam may be of use in patients with cUTI infected with certain ESBL-producing pathogens. On this basis, the indications have been separated with a cross-reference from complicated urinary tract infections to section 4.4 where the limitations of the evidence for use in cUTI are summarised in a paragraph.

Although the study CXA-cIAI-10-08 / CXA-cIAI-10-09 met its pre-defined primary endpoint, with supportive sensitivity analyses, the broad indication of cIAI based on this single pivotal study is poorly supported.

About half of ITT and CE patients had a primary focus of infection in the appendix compared to a maximum of 30% recommended in CHMP guidance. On this basis, it is not unexpected that half of the total patients received 4-7 days therapy. In ITT and ME populations the cure rates were very high for infections of appendiceal origin (e.g. ITT 89% ceftolozane/tazobactam and 92% meropenem) and much lower for infections originating from the colon (e.g. ITT 66% vs. 71%).

Since there is only one "not very satisfactory" study, the CHMP accepts the indication on condition of a cross-reference to section 4.4 SmPC, where the major limitations of the population studies are reflected, including the percentage with appendiceal infections, the low APACHE II scores and the few cases of accompanying bacteraemia.

2.6. Clinical safety

Patient exposure

The primary data to support the safety of ceftolozane/tazobactam come from the two Phase 3 studies. In Phase 3 studies ceftolozane/tazobactam was administered with metronidazole in the cIAI study, the comparators were different and the patient characteristics varied according to the type of infection (e.g. 70% female in cUTI but 41% in cIAI). Therefore it is important to review the safety data by indication as well as overall for the final selected dose regimen.

There were 1015 patients enrolled and treated in the Phase 3 studies, most of whom received 4-<8 (362 vs. 401 comparator) or 8-<11 (522 vs. 521) days of assigned treatment.

Adverse events

The safety profile in Phase 3 studies was broadly comparable between treatments within each indication. Overall rates of AEs did not increase with duration of therapy.

Table 43

Overall Summary of Treatment-emergent Adverse Events in the Integrated Phase 3 cUTI and cIAI Studies (Safety Population)

	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
Type of Adverse Event	Ceftolozane/ Tazobactam (N=533) n (%)	Levofloxacin (N=535) n (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n (%)	Meropenem (N=497) n (%)	Ceftolozane/ Tazobactam (N=1015) n (%)	All Comparators (N=1032) n (%)
Any TEAE	185 (34.7)	184 (34.4)	212 (44.0)	212 (42.7)	397 (39.1)	396 (38.4)
Any SAE	15 (2.8)	18 (3.4)	39 (8.1)	36 (7.2)	54 (5.3)	54 (5.2)
Any TEAE leading to Discontinuation of Study Drug	7 (1.3)	9 (1.7)	13 (2.7)	11 (2.2)	20 (2.0)	20 (1.9)
Any TEAE Resulting in Death	1 (0.2)	0	11 (2.3)	8 (1.6)	12 (1.2)	8 (0.8)
Any Treatment Related TEAE	55 (10.3)	64 (12.0)	39 (8.1)	44 (8.9)	94 (9.3)	108 (10.5)
Any Treatment Related SAE	2 (0.4)	0	1 (0.2)	1 (0.2)	3 (0.3)	1 (0.1)
Any Treatment Related TEAE leading to Discontinuation of Study Drug	3 (0.6)	6 (1.1)	3 (0.6)	4 (0.8)	6 (0.6)	10 (1.0)
Any Treatment Related TEAE Resulting in Death	0	0	0	0	0	0

Table 44

T eatment-emergent Adverse Events with an Incidence of ≥1% in the Integrated Phase 3 cUTI and cIAI Studies eftolozane/Tazobactam or Comparator Treatment Arm, by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
	Ceftolozane/ Tazobactam (N=533) n (%)	Levofloxacin (N=535) n (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n (%)	Meropenem (N=497) n (%)	Ceftolozane/ Tazobactam (N=1015) n (%)	All Comparators (N=1032) n (%)
Any Treatment-emergent Adverse Event	**185 (34.7)**	**184 (34.4)**	**212 (44.0)**	**212 (42.7)**	**397 (39.1)**	**396 (38.4)**
Gastrointestinal Disorders	63 (11.8)	61 (11.4)	98 (20.3)	84 (16.9)	161 (15.9)	145 (14.1)
Nausea	15 (2.8)	9 (1.7)	38 (7.9)	29 (5.8)	53 (5.2)	38 (3.7)
Diarrhoea	10 (1.9)	23 (4.3)	30 (6.2)	25 (5.0)	40 (3.9)	48 (4.7)
Constipation	21 (3.9)	17 (3.2)	9 (1.9)	6 (1.2)	30 (3.0)	23 (2.2)
Vomiting	6 (1.1)	6 (1.1)	16 (3.3)	20 (4.0)	22 (2.2)	26 (2.5)
Abdominal pain	4 (0.8)	2 (0.4)	6 (1.2)	2 (0.4)	10 (1.0)	4 (0.4)
Dyspepsia	1 (0.2)	4 (0.7)	2 (0.4)	7 (1.4)	3 (0.3)	11 (1.1)
General Disorders and Administration Site Conditions	27 (5.1)	21 (3.9)	50 (10.4)	43 (8.7)	77 (7.6)	64 (6.2)
Pyrexia	8 (1.5)	4 (0.7)	25 (5.2)	20 (4.0)	33 (3.3)	24 (2.3)
Oedema peripheral	3 (0.6)	4 (0.7)	9 (1.9)	4 (0.8)	12 (1.2)	8 (0.8)
Infections and Infestations	38 (7.1)	41 (7.7)	34 (7.1)	50 (10.1)	72 (7.1)	91 (8.8)
Urinary tract infection	9 (1.7)	9 (1.7)	4 (0.8)	2 (0.4)	13 (1.3)	11 (1.1)
Nervous System Disorders	41 (7.7)	33 (6.2)	28 (5.8)	21 (4.2)	69 (6.8)	54 (5.2)
Headache	31 (5.8)	26 (4.9)	12 (2.5)	9 (1.8)	43 (4.2)	35 (3.4)
Dizziness	6 (1.1)	1 (0.2)	4 (0.8)	5 (1.0)	10 (1.0)	6 (0.6)
Metabolism and Nutrition Disorders	12 (2.3)	17 (3.2)	39 (8.1)	34 (6.8)	51 (5.0)	51 (4.9)
Hypokalaemia	4 (0.8)	2 (0.4)	14 (2.9)	8 (1.6)	18 (1.8)	10 (1.0)
Hypoalbuminaemia	0	2 (0.4)	7 (1.5)	8 (1.6)	7 (0.7)	10 (1.0)
Vascular Disorders	22 (4.1)	17 (3.2)	25 (5.2)	23 (4.6)	47 (4.6)	40 (3.9)
Hypertension	16 (3.0)	7 (1.3)	9 (1.9)	10 (2.0)	25 (2.5)	17 (1.6)
Hypotension	2 (0.4)	1 (0.2)	8 (1.7)	4 (0.8)	10 (1.0)	5 (0.5)
Psychiatric Disorders	11 (2.1)	18 (3.4)	34 (7.1)	28 (5.6)	45 (4.4)	46 (4.5)
Insomnia	7 (1.3)	14 (2.6)	17 (3.5)	11 (2.2)	24 (2.4)	25 (2.4)
Anxiety	1 (0.2)	4 (0.7)	9 (1.9)	7 (1.4)	10 (1.0)	11 (1.1)
Respiratory, Thoracic, and Mediastinal Disorders	6 (1.1)	10 (1.9)	32 (6.6)	36 (7.2)	38 (3.7)	46 (4.5)
Pleural effusion	1 (0.2)	0	9 (1.9)	7 (1.4)	10 (1.0)	7 (0.7)
Cough	3 (0.6)	5 (0.9)	1 (0.2)	6 (1.2)	4 (0.4)	11 (1.1)
Investigations	12 (2.3)	13 (2.4)	23 (4.8)	21 (4.2)	35 (3.4)	34 (3.3)
Alanine aminotransferase increased	9 (1.7)	5 (0.9)	7 (1.5)	5 (1.0)	16 (1.6)	10 (1.0)
Aspartate aminotransferase increased	9 (1.7)	5 (0.9)	5 (1.0)	3 (0.6)	14 (1.4)	8 (0.8)
Blood and Lymphatic System Disorders	9 (1.7)	10 (1.9)	19 (3.9)	16 (3.2)	28 (2.8)	26 (2.5)
Thrombocytosis	2 (0.4)	2 (0.4)	9 (1.9)	5 (1.0)	11 (1.1)	7 (0.7)
Injury, Poisoning and Procedural Complications	2 (0.4)	2 (0.4)	26 (5.4)	32 (6.4)	28 (2.8)	34 (3.3)
Anaemia postoperative	0	0	10 (2.1)	8 (1.6)	10 (1.0)	8 (0.8)
Cardiac Disorders	3 (0.6)	5 (0.9)	21 (4.4)	15 (3.0)	24 (2.4)	20 (1.9)
Tachycardia	0	2 (0.4)	7 (1.5)	9 (1.8)	7 (0.7)	11 (1.1)
Musculoskeletal and Connective Tissue Disorders	9 (1.7)	15 (2.8)	6 (1.2)	14 (2.8)	15 (1.5)	29 (2.8)
Arthralgia	1 (0.2)	6 (1.1)	0	4 (0.8)	1 (0.1)	10 (1.0)

The reporting rates were consistently higher with ceftolozane/tazobactam in both indications for nausea, constipation, abdominal pain, pyrexia, headache, hypotension, hypokalaemia and for each of ALT and AST increased. Administration site events were reported in <1% of subjects.

Most TEAEs occurred within 72 hours of starting study drug (in 70% and 68% of patients reporting AEs in respective treatment groups, pooled across studies) and the majority were documented to have resolved (in 79% and 77% with TEAEs). Less than 15% of patients had drug-related TEAEs reported by investigators. The most common were nausea, diarrhoea, headache and transaminase increases.

Table 45

T rug-Related Treatment-emergent Adverse Events by Preferred Term ccurring in ≥1% of Subjects in Either Treatment Arm the Integrated Phase 3 cUTI and cIAI Studies (Safety Population)

	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
Preferred Term	Ceftolozane/ Tazobactam (N=533) n (%)	Levofloxacin (N=535) n (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n (%)	Meropenem (N=497) n (%)	Ceftolozane/ Tazobactam (N=1015) n (%)	All Comparators (N=1032) n (%)
Any treatment-related TEAE	55 (10.3)	64 (12.0)	39 (8.1)	44 (8.9)	94 (9.3)	108 (10.5)
Nausea	7 (1.3)	3 (0.6)	10 (2.1)	3 (0.6)	17 (1.7)	6 (0.6)
Diarrhoea	4 (0.8)	19 (3.6)	12 (2.5)	12 (2.4)	16 (1.6)	31 (3.0)
Headache	10 (1.9)	5 (0.9)	4 (0.8)	0	14 (1.4)	5 (0.5)
AST increased	7 (1.3)	4 (0.7)	3 (0.6)	3 (0.6)	10 (1.0)	7 (0.7)

The applicant also generated a list of ADRs after review of TEAEs in the Phase 3 studies for possible causal relationship, taking into account known class effects. This list showed higher rates with ceftolozane/tazobactam in both studies for headache, nausea, constipation, abdominal pain and AST/ALT increased.

An additional review of AESIs was conducted. Anaphylaxis and haemolytic disorders were not observed with ceftolozane/tazobactam in Phase 3 studies.

- Eleven (1.1%) ceftolozane/tazobactam and 8 (0.8%) comparator patients had acute renal failure reported but only one per treatment group was considered drug-related. The PTs revealed that renal impairment was reported in 6 vs. 3 and (acute) renal failure in 4 vs. 1 in respective groups.
- PMC was reported for 0.4% (n=4) ceftolozane/tazobactam and 0.3% (n=3) comparator patients. The 4 in ceftolozane/tazobactam patients were of moderate severity but 3 were SAEs.
- Eight ceftolozane/tazobactam (0.8%) and 11 (1.1%) comparator patients had at least 1 thrombophlebitis TEAE and these were considered drug-related in 3 vs. 6 cases. All thrombophlebitis events were mild or moderate in severity.

In the Phase 3 studies 7 AEs of rash were reported in ceftolozane/tazobactam patients and 5 in the comparator groups. None was serious, 10/12 were mild in severity and one rash per treatment group was of moderate severity. In all cases, the rashes began after multiple days of exposure to study drug. In ceftolozane/tazobactam patients the time to onset was between day 3 and day 6. No action was taken with study drug for any of the rashes in ceftolozane/tazobactam patients but treatment was required in 4 cases in each treatment group.

Further explorations of the database did not suggest higher rates of AEs for ceftolozane vs. comparators in subgroups such as those with renal impairment of the elderly.

Serious adverse event/deaths/other significant events

Deaths

In Phase 3 studies there were 12 deaths in ceftolozane/tazobactam patients and 8 in comparator patients, most (11 vs. 8) of which occurred in the cIAI study. Seven subjects died while on study therapy or within 24 h of termination of study drug. None was considered related to study drug. The causes of death in the ceftolozane/ tazobactam group were pneumonia, multi-organ failure (3), obstructive renal failure, cardiac failure (2), myocardial infarction and sudden death (2). In the meropenem group the causes of death were infection (of skin graft on amputated leg), circulatory collapse, road traffic accident, septic shock (2), pulmonary embolism and cardiac insufficiency and myocardial infarction.

SAEs

There was a higher incidence of SAEs in the cIAI indication but within each study there were no obvious differences between treatments. In the cUTI study *C. difficile* colitis and PMC in ceftolozane/tazobactam patients were considered drug-related. In the cIAI study 10 and 12 SAEs were associated with clinical failure and two cases (one per group) of *C. difficile* colitis were considered drug-related.

Table 46

ious Treatment-emergent Adverse Events by Preferred Term Occurring in More than One Subject in the Integrated ase 3 cUTI and cIAI Studies (Safety Population)

	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
Preferred Term	Ceftolozane/ Tazobactam (N=533) n (%)	Levofloxacin (N=535) n (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n (%)	Meropenem (N=497) n (%)	Ceftolozane/ Tazobactam (N=1015) n (%)	All Comparators (N=1032) n (%)
Any Serious Treatment-emergent Adverse Event	15 (2.8)	18 (3.4)	39 (8.1)	36 (7.2)	54 (5.3)	54 (5.2)
Urinary tract infection	3 (0.6)	2 (0.4)	1 (0.2)	0	4 (0.4)	2 (0.2)
Abdominal abscess	1 (0.2)	0	2 (0.4)	2 (0.4)	3 (0.3)	2 (0.2)
Multi-organ failure	0	0	3 (0.6)	0	3 (0.3)	0
Septic shock	0	0	3 (0.6)	2 (0.4)	3 (0.3)	2 (0.2)
Bladder cancer	2 (0.4)	0	0	0	2 (0.2)	0
Clostridium difficile colitis	1 (0.2)	0	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.1)
Ischaemic stroke	0	0	2 (0.4)	0	2 (0.2)	0
Pneumonia	2 (0.4)	0	0	2 (0.4)	2 (0.2)	2 (0.2)
Sudden death	0	0	2 (0.4)	0	2 (0.2)	0
Urosepsis	2 (0.4)	0	0	0	2 (0.2)	0
Wound evisceration	0	0	2 (0.4)	0	2 (0.2)	0
Acute respiratory distress syndrome	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Anastomotic leak	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Cardiac failure	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Ileus	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Liver abscess	1 (0.2)	0	0	3 (0.6)	1 (0.1)	3 (0.3)
Myocardial infarction	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Nausea	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Pelvic abscess	0	0	1 (0.2)	2 (0.4)	1 (0.1)	2 (0.2)
Pseudomembranous colitis	1 (0.2)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Respiratory distress	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Respiratory failure	0	0	1 (0.2)	2 (0.4)	1 (0.1)	2 (0.2)
Small intestinal obstruction	0	0	1 (0.2)	2 (0.4)	1 (0.1)	2 (0.2)
Wound dehiscence	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Bile duct stone	0	0	0	2 (0.4)	0	2 (0.2)
Pyelonephritis	0	6 (1.1)	0	0	0	6 (0.6)
Sepsis	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)
Subdiaphragmatic abscess	0	0	0	2 (0.4)	0	2 (0.2)
Transient ischaemic attack	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)

Laboratory findings

In Phase 3 studies, shifts in haematology findings of 2 or more grades from baseline to any post-baseline assessment were observed for 11% in the ceftolozane/tazobactam group and 8% in the comparator group. In Phase 3 two ceftolozane/tazobactam patients seroconverted from a negative to positive Coombs' test at the EOT visit but there were no findings to indicate haemolytic anaemia. Additional cases occurred in Phase 1 and 2 studies but without findings indicative of haemolytic anaemia.

Shifts in chemistry findings of 2 or more grades from baseline to any post-baseline assessment were observed at comparable rates between treatments. Shifts from Grade 0, 1 or 2 at baseline to a worst value post-baseline of Grade 3 or 4 were generally uncommon for chemistry parameters. In the cIAI indication, shifts to Grade 3 or 4 were most commonly observed for GGT (9% ceftolozane/tazobactam vs. 13% meropenem), low phosphate (4% vs. 7%) and increased AST (3% vs. 2%).

The incidence of ALT or AST elevations >3×ULN was low at ~1% for both treatments across studies. The incidence of hepatic enzyme elevations >3×ULN in the cIAI study was 2% for ceftolozane/tazobactam vs. <1% for meropenem. One subject in the ceftolozane/tazobactam group met the criteria for Hy's law on study Day 3 but also met the criteria at screening and values declined while on therapy. In the Phase 2 study in cIAI one subject with cholecystitis in the ceftolozane/tazobactam group met the laboratory criteria for Hy's law during treatment (Day 2). The patient had a baseline elevation in ALT, AST and total bilirubin and levels declined during continued treatment with ceftolozane/tazobactam.

In the Phase 3 studies the applicant's review of AESIs revealed that 11 (1.1%) ceftolozane/tazobactam patients and 8 (0.8%) comparator patients had acute renal failure reported but only one per treatment group was considered drug-related. The PTs revealed that renal impairment was reported in 6 vs. 3 and (acute) renal failure was reported in 4 vs. 1 in respective groups. At TOC the data indicate that 15 patients with a normal baseline level had Grade 1, 2 or 4 elevations at TOC while two had an increase from Grade 1 to 2. For the pooled comparators, there were 19 patients with shifts from normal baseline to Grade 1 (16) or 2 (3) elevations at TOC.

Table 47

Parameter (SI unit) / Visit / Toxicity Grade	Ceftolozane/Tazobactam (N=1015) Baseline Toxicity Grade n (%) Normal	Grade 1	Grade 2	Grade 3	Grade 4	Missing	All Comparators (N=1032) Baseline Toxicity Grade n (%) Normal	Grade 1	Grade 2	Grade 3	Grade 4	Missing
Creatinine (umol/L) (continued)												
TOC, N1	784	74	36	2	0	33	800	88	28	1	0	33
Normal	769 (98.1)	52 (70.3)	12 (33.3)	1 (50.0)	0	32 (97.0)	781 (97.6)	57 (64.8)	13 (46.4)	1 (100)	0	32 (97.0)
Grade 1	13 (1.7)	20 (27.0)	8 (22.2)	0	0	1 (3.0)	16 (2.0)	26 (29.5)	6 (21.4)	0	0	0
Grade 2	1 (0.1)	2 (2.7)	16 (44.4)	1 (50.0)	0	0	3 (0.4)	4 (4.5)	9 (32.1)	0	0	0
Grade 3	0	0	0	0	0	0	0	1 (1.1)	0	0	0	1 (3.0)
Grade 4	1 (0.1)	0	0	0	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0	0	0

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine	<1.1×ULN	1.1-1.5×ULN	>1.5-3.0×ULN	>3-6×ULN	>6×ULN

Safety in special populations

Gender

There was no relevant gender difference in the incidence or types of TEAS, SAEs or events leading to discontinuation.

Age

In Phase 3 studies 250 ceftolozane/tazobactam patients were aged ≥ 65 years and 113 were ≥ 75 years. Generally and in both treatment groups the incidence of TEAEs, SAEs, discontinuations due to TEAEs and deaths tended to be higher among those aged > 65 years and for those aged >75 vs. 65-74 years. Types of events that were more commonly reported in the elderly were spread across several SOCs and no qualitative difference in the AE profile was identified in the elderly population.

Race

As approximately 90% were White and predominantly Eastern European, a meaningful analysis of racial differences is not possible.

BMI

In Phase 3 studies 484/2047 (24%) had BMI ≥30 kg/m^2. There was no relevant difference in the incidence of individual TEAEs reported between the BMI subgroups.

Discontinuation due to adverse events

In Phase 3 studies 20 patients per treatment group discontinued study drug because of TEAEs. Those TEAEs triggering discontinuation that occurred in more than one patient are shown below.

Table 48

T: eatment-emergent Adverse Events by Preferred Term Leading to Discontinuation of Study Drug in More than 1 bject in the Integrated Phase 3 cUTI and cIAI Studies (Safety Population)

	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
Preferred Term	Ceftolozane/ Tazobactam (N=533) n (%)	Levofloxacin (N=535) n (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n (%)	Meropenem (N=497) n (%)	Ceftolozane/ Tazobactam (N=1015) n (%)	All Comparators (N=1032) n (%)
Any TEAE Leading to Study Drug Discontinuation	7 (1.3)	9 (1.7)	13 (2.7)	11 (2.2)	20 (2.0)	20 (1.9)
Renal impairment[a]	2 (0.4)	0	3 (0.6)	0	5 (0.5)	0
Diarrhoea	0	2 (0.4)	1 (0.2)	0	1 (0.1)	2 (0.2)
Clostridium difficile colitis	0	0	0	2 (0.4)	0	2 (0.2)
Drug hypersensitivity	0	2 (0.4)	0	0	0	2 (0.2)
Dermatitis allergic	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)

The 5 patients who discontinued ceftolozane/tazobactam because of renal impairment/renal failure had at least mild renal impairment at baseline. The protocol required subjects to discontinue therapy if CRCL decreased below 30 mL/min while on therapy.

2.6.1. Discussion on clinical safety

A total of 2076 subjects were randomised into the Phase 3 studies, including 1083 in the cUTI indication and 993 in the cIAI indication; 2047 (99%) of these subjects were treated with study drug and are included in the Safety population. Overall in the integrated analysis, 1015 subjects (49.6%) were treated with ceftolozane/tazobactam (with or without metronidazole) and 1032 (50.4%) were treated with a comparator. Across the two Phase 2 studies, a total of 251 subjects were randomised and 248 subjects received study drug (167 received ceftolozane or ceftolozane/tazobactam). The majority of treated subjects completed study participation (95%) and completed study drug treatment (86%). Across the 9 Phase 1 studies, a total of 305 subjects were enrolled and received study drug. The majority of treated subjects completed study drug (98%). In all studies, there was no notable difference between treatment arms in the study completion rates. Overall, the extent of exposure to study therapy was similar between subjects in the ceftolozane/tazobactam and comparator treatment arms. Although the treatment regimens were different between the 2 indications, the median duration of therapy was similar in both (6.7 days in the cUTI indication and 6.2 days in the cIAI indication). Ceftolozane/tazobactam was administered as a single dose up to 4.5 g and multiple doses up to 9 g daily for up to 10 days in the Phase 3 studies. The applicant is asked to compare the number and types of the AEs in patients who were treated until one week versus 7-14 days.

The number of patients with the target indications, exposed to ceftolozane/tazobactam at the recommended dosage is considered acceptable to adequately evaluate the safety profile.

In the integrated Phase 3 analysis, the majority of subjects were White/Caucasian and from Eastern Europe, more than half (56%) of all subjects were female, and the median age was 51 to 52 years. Overall, 24% of subjects were elderly (≥65 years of age) and 56 (11.8 %) of these patients in the ITT population were ≥75 years. There is limited clinical data on the use of ceftolozane/tazobactam in elderly patients > 75 year.

In the cUTI indication, 70% of subjects were female and in the cIAI 59% of the patients were male. Overall, there was no major imbalance in demographic characteristics between ceftolozane/tazobactam and levofloxacin and meropenem groups.

Most TEAEs for ceftolozane/tazobactam were of mild to moderate severity. Overall, the prevalence of TEAEs was comparable and almost similar for the study drug versus comparators.

The most common treatment-emergent adverse events (TEAE) in the ceftolozane/tazobactam arms in the phase 3 studies were typical for hospitalized subjects treated with cephalosporins and included nausea (5.2%), diarrhea (3.9%), constipation (3.0%), vomiting (2.2%), pyrexia (3.3%), headache (4.2%), insomnia (2.4%), and transaminase increases (ALT 1.%, AST 1.4%). Based on the available data, the applicant has included adequate information regarding most of these adverse events and the frequencies for each event for the intended dosage recommendation in SmPC 4.8.

The TEAEs for the comparators in the integrated phase 3 cUTI and cIAI were as follow: nausea (3.7%), diarrhea (4.7%), constipation (2.2%), vomiting (2.5%), pyrexia (2.3%), headache (3.4%), insomnia (2.4%), and transaminase increases (ALT 1.0%, AST 0.8%). Generally, there are similar TEAEs with similar prevalence when comparing drug study versus comparator.

In the integrated Phase 3 studies, 12 subjects in the ceftolozane/tazobactam treatment arm and 8 subjects (including one in road traffic accident) in the comparator treatment arm died during or shortly after treatment. Except for one, all deaths were in cIAI patients as was to be expected considering the increased severity of cIAIs compared with cUTIs. Most of the patients who died were ≥ 65 years (9 in ceftolozane vs 4 in meropenem).

The incidence of SAEs was similar in the integrated ceftolozane/tazobactam treatment arm (54 subjects, 5.3%) and the comparator treatment arm (54 subjects, 5.2%). There was a higher incidence of SAEs in the cIAI indication consistent with the severity of the disease and surgical intervention. Most SAEs were single events and were most commonly reported in the Infections and Infestations SOC, like urinary tract infections (0.4%), abdominal abscess (0.3%), and septic shock (0.3%). The applicant is asked to discuss the causative bacteria and the resistance profiles involved in the infections and infestations in the ceftolozane/tazobactam groups. Overall, the incidence of other SAEs was low and balanced across treatment arms in the clinical programme.

No haemolytic disorders were reported and no subject treated with ceftolozane/tazobactam in the integrated Phase 3 studies experienced an anaphylactic reaction. Memberanous colitis, including incidence of events related to *C. difficile*, potential for thrombophlebitis or infusion-related TEAEs, and renal toxicity with ceftolozane/tazobactam therapy are considered low and comparable between ceftolozane/tazobactam and comparator groups.

There were no significant changes at baseline and post-baseline in any of the laboratory parameters. In total one subject in the Phase 3 studies (treated with ceftolozane/tazobactam) was identified as fulfilling the criteria for Hy's law. According to the inclusion criteria for the study, subjects with high transaminases values should not be included in the study. There is no data suggesting that the hepatotoxicity is related to treatment with ceftolozane/tazobactam. In the Phase 2 study CXA-IAI-10-01 (cIAI), one subject in the ceftolozane/tazobactam treatment arm met the criteria for Hy's law during the treatment period (Day 2). Again, there are no data which indicate that the hepatotoxicity is related to treatment with ceftolozane/tazobactam.

The incidence of elevation of both ALT and in particular AST was higher in the ceftolozane/tazobactam than the comparator arms. This issue has been adequately reflected in the SmPC Section 4.8. There is no evidence for an increased risk of hepatotoxicity related to treatment with ceftolozane/tazobactam from the presented data. The changes for other chemistry parameters are low and comparable between the study drug and the comparators.

Overall, there were no clinically meaningful changes in systolic and diastolic BP, heart rate, and temperature from baseline ceftolozane/tazobactam and comparator treatment arms. The TQT study was negative, with no findings indicating an effect of ceftolozane/tazobactam on cardiac repolarisation.

The types of events that were more commonly reported in elderly subjects in cIAI included events in the General Disorders and Administration Site Conditions, Cardiac Disorders, Metabolism and Nutritional Disorders, Renal and Urinary Disorders, Vascular Disorders, and Psychiatric Disorders SOCs. The applicant is asked to specify the TEAEs within each event.

Overall, 494 (24%) of the 2047 subjects in the integrated analyses were ≥65 years of age providing an adequate sample for analysis of safety in the elderly. Slightly more adverse events are observed in older subjects with cIAI, which could be reflective of the nature of the indication and their physiological status.

No notable differences across treatment arms were observed between male and female subjects and subjects with high and normal BMI in the overall incidence or types of TEAEs. Analysis of TEAEs by race revealed no consistent differences across treatment arms in the integrated Phase 3 studies between White, Black/African American, Asian, or other subjects. Results of the analysis of TEAEs by race were similar between treatment arms and in both indications. However, as approximately 90% of subjects in both treatment arms were White and predominantly Eastern European, the widespread applicability of the results of this analysis is somewhat limited.

In the Phase 3 studies, the types of events that were more commonly reported in subjects with moderate renal impairment at baseline compared with those with normal renal function or mild impairment were distributed across multiple body systems. In the Phase 1 study CXA-101-02, the incidence of TEAEs was 4 of 6 (67%) subjects with mild renal impairment and 1 of 6 (17%) subjects with normal renal function. TEAE in these patient groups have been presented on System Organ Class (SOC).

Based on the clinical and non-clinical evaluations, the potential for clinically relevant Drug-Drug Interactions (DDIs) with ceftolozane/tazobactam is considered low**.**

Overall, in the Phase 3 studies discontinuations of study drug due to TEAEs were similar between treatment arms; 20 (2.0%) vs 20 (1.9%) subjects. Discontinuation was also low and comparable between the ceftolozane/tazobactam arm and the comparator arms in the submitted Phase 2 studies.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

A dose or exposure relationship to safety could not be identified for ceftolozane/tazobactam as all patients received the same dose and plasma exposures were not measured in Phase 3.

The Phase 3 studies do not suggest a marked difference in the safety profile between ceftolozane/tazobactam and respective comparators within each of the two indications but there were some differences in rates. In particular, reporting rates were consistently higher with ceftolozane/tazobactam in both indications for nausea, constipation, abdominal pain, pyrexia, headache, hypotension, hypokalaemia and for each of ALT and AST increased.

A positive Coombs test was recorded in a number of patients, although there was no evidence of associated haemolytic anaemia. There are no major concerns raised by the small difference in numbers of deaths or by the distribution of numbers and types of SAEs.

The overall reported rate of transaminase abnormalities was higher for ceftolozane/tazobactam but the differences were not marked. Although two patients have met Hy’s law criteria it seems unlikely that

either case was directly due to ceftolozane/tazobactam. There was an imbalance in renal TEAEs, which in most cases seem to reflect changes in serum creatinine.

There are no major concerns regarding safety.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Hypersensitivity reactions • *Clostridium difficile*-associated diarrhoea • Renal impairment • Medication errors
Important potential risks	• Emergence of bacterial resistance to ceftolozane/tazobactam • Severe skin reactions • Haemolytic anaemia
Missing information	• Safety and efficacy in paediatric patients < 18 years old • Experience in pregnant or lactating women • Safety and efficacy in immunocompromised patients • Off-label use

Pharmacovigilance plan

No additional pharmacovigilance activities are proposed.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Hypersensitivity reactions	Contraindication in section 4.3 of the SmPC with respect to hypersensitivity to the active substances or to any of the excipients or if the patient has known serious hypersensitivity to ceftolozane/tazobactam, piperacillin/tazobactam, or members of the cephalosporin class. Warning in Section 4.4 of the SmPC that serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible and that patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to ceftolozane/tazobactam. Ceftolozane/tazobactam should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or any other type of beta-lactam antibacterial agent. Rash is included as a uncommon undesirable effect in Section 4.8 of the SmPC.	None
***Clostridium difficile*-associated diarrhoea**	Warning in section 4.4 of the SmPC concerning CDAD informing that antibacterial-associated colitis and pseudomembranous colitis have been reported with ceftolozane/tazobactam and that it is important to consider CDAD diagnosis in patients who present with diarrhoea during or subsequent to the administration of ceftolozane/tazobactam. *Clostridium difficile* colitis is included as an uncommon undesirable effect in SmPC Section 4.8.	None
Renal impairment	Dose adjustments for patients with moderate or severe renal impairment and patients with end stage renal disease are recommended in section 4.2 of the SmPC.	None
Medication errors	Posology and method of administration is included in Section 4.2 of the SmPC.	None
Important Potential Risks		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Emergence of bacterial resistance to ceftolozane/tazobactam	Advice in section 4.1 of the SmPC that guidance on the appropriate use of antibacterial agents should be considered. Information concerning bacterial resistance mechanisms and recommendation that expert advice should be sought when the local prevalence of resistance is such that the utility of ceftolozane/tazobactam in at least some types of infections is questionable are included in section 5.1 of the SmPC.	None
Severe skin reactions	Contraindication in section 4.3 of the SmPC with respect to hypersensitivity to the active substances or to any of the excipients or if the patient has known serious hypersensitivity to ceftolozane/tazobactam, piperacillin/tazobactam, or members of the cephalosporin class. Warning in Section 4.4 of the SmPC that serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible and that patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to ceftolozane/tazobactam. Ceftolozane/tazobactam should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or any other type of beta-lactam antibacterial agent. Rash is included as a uncommon undesirable effect in Section 4.8 of the SmPC.	None
Haemolytic anaemia	Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia is included in SmPC Section 4.4 Special warnings and precautions for use.	None
Missing Information		
Safety and efficacy in paediatric patients < 18 years old	In section 4.1 of the SmPC it is stated that ceftolozane/tazobactam is indicated for the treatment of the following infections in adults: - Complicated intra-abdominal infections in combination with metronidazole - Complicated urinary tract infections - Acute pyelonephritis. In section 4.2 of the SmPC it is stated that the safety and efficacy of ceftolozane/tazobactam in children less than 18 years of age has not yet been established and that no data are available.	None
Experience in pregnant or lactating women	In section 4.6 of the SmPC it is stated that there are no data from the use of ceftolozane/tazobactam in pregnant women and that ceftolozane/tazobactam should only be used during pregnancy if clearly indicated, i.e., only if the expected benefit outweighs the possible risks to the pregnant woman and foetus. In addition, it states that ceftolozane and tazobactam concentrations in human milk have not been studied. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.	None
Safety and efficacy in immunocompromised patients	Section 4.4 of the SmPC warns that experience of using ceftolozane/tazobactam in patients who are severely immunocompromised, receiving immunosuppressive therapy and patients with severe neutropenia is limited since this population was excluded from Phase 3 trials.	None
Off-label use	In section 4.1 of the SmPC it is stated that ceftolozane/tazobactam is indicated for the treatment of the following infections in adults: - Complicated intra-abdominal infections in combination with metronidazole - Complicated urinary tract infections - Acute pyelonephritis	None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Given the small size of the vial label and the fact that the product is to be administered by healthcare professionals only (Art. 63.3), the QRD Group has accepted the request to have only the minimum particulars displayed on the vial label with the following comments:

- Short term for the pharmaceutical form should be "Powder for concentrate"

- The route of administration should be "For IV use after reconstitution and dilution".

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zerbaxa (ceftolozane / tazobactam) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of ceftolozane/tazobactam was evaluated in two Phase 3 studies, each of which was formed by merging of two initial studies in two types of infection. The overall pre-defined primary analyses in each study demonstrated non-inferiority for ceftolozane/tazobactam against selected comparative regimens

Uncertainty in the knowledge about the beneficial effects.
Ceftolozane has been developed only in a FDC. To justify this presentation it is essential that the tazobactam dose is considered adequate to protect ceftolozane from hydrolysis by beta-lactamases potentially within the inhibitory range of tazobactam. The clinical data alone do not support such a conclusion due to the nature of the indications studied (i.e., cIAI in which surgery plays a major therapeutic role; UTI being the easiest to treat due to high urinary levels of ceftolozane and tazobactam) and the limited range of beta-lactamases that were produced by the patient isolates. Therefore the final conclusion on the adequacy of the tazobactam dose to treat a broad range of beta-lactamase-producing organisms rests on the non-clinical evidence to support the sufficiency of 0.5 g q8h when used in conjunction with ceftolozane. This matter was investigated further during the application procedure with a final conclusion that the dose is likely adequate for most Class A enzymes within the range of tazobactam but it may not suffice even for these enzymes if they are hyper-produced. Additional text was drafted for section 5.1 of SmPC to convey these limitations.

The Addendum to Guideline CPMP/EWP/558/95 Rev 2 states that it is preferable to evaluate efficacy against cUTI and acute pyelonephritis in separate studies. If they are evaluated in the same study then stratification at randomisation with capping of the proportion with pyelonephritis is recommended. In the applicant's UTI study, 82% in the ME population had pyelonephritis. This is then reflected in the population demographics. For example, in the ceftolozane/tazobactam group with pyelonephritis 81% of patients were female, 81% were 18-65 years and 66% had normal renal function whereas in the small group with cUTI 72% were male, 53% were aged 18-65 years and 43% had normal renal function.

Within the pyelonephritis sub-population ceftolozane/tazobactam was non-inferior to levofloxacin. In the small numbers of patients with cUTI the success rates numerically favoured ceftolozane/tazobactam, even after excluding cases due to organisms that were resistant to levofloxacin, but no conclusions can be drawn regarding non-inferiority of ceftolozane/tazobactam vs. levofloxacin.

In light of the doubt regarding the dose of tazobactam, it is important to note that eradication rates in urine were impacted by the presence of certain beta-lactamases despite the anticipated high drug concentrations predicted in the urinary tract. It is clear that some of these beta-lactamases are not within the range of inhibition of tazobactam. However, in some cases, failure was associated with hyper-production of enzymes that could be inhibited by tazobactam subject to a sufficient dose regimen.

In the cIAI study near to half of ITT and CE patients had a primary focus of infection in the appendix compared to a maximum of 30% recommended in the Addendum to Guideline CPMP/EWP/558/95 Rev 2 . The patient demographics, including the low APACHE scores and the fact that half of the total patients received 4-7 days therapy, reflect the predominant underlying diagnosis. Therefore the study population was not adequately representative of the range of infections encompassed under the cIAI indication.

Added to the concerns is that point estimate cure rates were numerically lower for ceftolozane/tazobactam and meropenem in those with APACHE scores > 10 (most of whom had non-appendiceal primary infection), in patients aged > 65 years (in whom the primary site of infection was more often the bowel) and in those with multiple abscess or diffuse peritonitis. Correlating with these findings, the failures in the ceftolozane/tazobactam group were more likely to be elderly subjects (44.2% of ceftolozane failures vs. 27.1% meropenem failures), have peritonitis (76.6% vs. 64.3%) and have had a laparotomy (64.9% vs. 48.6%). These results in subgroups contributed to a fairly consistent numerical inferiority for ceftolozane/tazobactam vs. meropenem despite the fact the primary analysis demonstrated non-inferiority according to the pre-defined criteria.

Thus, the populations studied did not meet the CHMP expectations as laid down in the "Addendum to Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 2)" and for cUTI and intra-abdominal infections the data are still considered to be suboptimal. However, these indications have been accepted by CHMP, subject to adequate reflection of the limitations of these data in the SmPC.

In addition, in both indications cure rates tended to be lower in those with moderate renal impairment at baseline. This observation affected both treatment groups. Nevertheless, it seems appropriate to recommend frequent monitoring of renal function in those with moderate renal impairment at baseline so that prompt dose adjustments may be made in case of rapid recovery in renal function during treatment.

Risks

Unfavourable effects

Ceftolozane/tazobactam appears to be associated with TEAEs that are typical and expected of beta-lactam agents. There are no additional signals of major concern at this time to suggest that the FDC would be associated with additional and unexpected risk for these types of agents.

The Phase 3 studies compared ceftolozane/tazobactam with levofloxacin or meropenem. Although there was not a marked difference in the safety profile between ceftolozane/tazobactam and respective comparators the AE reporting rates were consistently higher with ceftolozane/tazobactam in both indications for nausea, constipation, abdominal pain, pyrexia, headache, hypotension, hypokalaemia and for each of ALT and AST increased. Most of these AEs also figured among events considered drug-related by investigators and identified in the applicant's review of the database for likely ADRs.

Uncertainty in the knowledge about the unfavourable effects

The overall reported rate of transaminase abnormalities was higher for ceftolozane/tazobactam but the differences were not marked. Although two patients have met Hy's law criteria it seems unlikely that either case was directly due to ceftolozane/tazobactam. There was also an imbalance in renal TEAEs, which in most cases seem to reflect changes in serum creatinine but the differences were not so marked as to represent a major concern.

Benefit-risk balance

Importance of favourable and unfavourable effects

Ceftolozane/tazobactam combines a new beta-lactam with an old inhibitor that has severe limitations in its range of beta-lactamase inhibition. However, at the right dose, tazobactam may serve to protect ceftolozane from some ESBLs that could otherwise hydrolyse the beta-lactam.

Ceftolozane itself may have some utility in treating a small number of *P. aeruginosa* that are resistant to several other agents via specific mechanisms but tazobactam does not influence the activity of ceftolozane against such strains.

It is important that the specific infection types which have been studied and hence the limitations of the data are adequately reflected in the SmPC.

Benefit-risk balance

Discussion on the benefit-risk balance

Ceftolozane is a semisynthetic, parenteral antibacterial agent of the cephalosporin class with the usual mechanism of bactericidal activity of the beta-lactams. The spectrum of activity of ceftolozane includes enterobacteria, several non-fermenters, fastidious Gram-negative organisms, some streptococci and a few selected anaerobes. Ceftolozane alone is stable in the presence of those beta-lactamases that generally do not hydrolyse cephalosporins (such as TEM-1) but it is readily hydrolysed by a wide range of ESBLs and by AmpC enzymes produced by some genera, such as *Enterobacter spp*. It is unusual for its relative stability in the presence of pseudomonal AmpC enzymes. Also, it is not affected by loss of OprD by *P. aeruginosa* and it is a poor substrate for pseudomonal efflux pumps.

Ceftolozane represents a new active substance. It has been developed for clinical use only as part of a FDC presentation with a beta-lactamase inhibitor (tazobactam) that has been on the market (as part of a FDC with piperacillin) since the early 1990s.

Tazobactam acid is a penicillanic acid sulfone derivative which can inhibit a range of bacterial class A and some class C β-lactamases. Tazobactam can potentially protect ceftolozane from hydrolysis by some beta-lactamases, broadening its spectrum to include a range of ESBL-producing *E. coli, K. pneumoniae* and other *Enterobacteriaceae*. However, tazobactam does not have useful inhibitory activity against many problematic beta-lactamases, such as several of the class C enzymes, the carbapenemases (serine-based and metallo-enzymes) or Class D enzymes.

Based on single pivotal studies, the CHMP accepts Zerbaxa for treatment of the following infections in adults:

- Complicated intra-abdominal infections (see section 4.4);
- Acute pyelonephritis;
- Complicated urinary tract infections (see section 4.4).

at an agreed posology of 1 g ceftolozane and 0.5 g tazobactam q8h for a fixed duration of 7 days in cUTI and acute pyelonephritis and a range from 4-14 days in cIAI, with caveat of dose adjustment in case of moderate or severe renal impairment or end stage renal disease requiring haemodialysis. The Product Information describes the limitations of the data supporting cUTI and cIAI indications (see section 4.4 SmPC).

Although PK-PD justification for the tazobactam dose was not robust, data suggests that provided the susceptibility breakpoint for enterobacteria is no more than 1 mg/L, the tazobactam dose may suffice to cover the majority of the common Class A enzymes.

Ceftolozane/tazobactam appears to be associated with TEAES that are typical and expected of beta-lactam agents. There are no additional signals of major concern at this time to suggest that the FDC would be associated with additional and unexpected risk for these types of agents.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zerbaxa in the treatment of the following infections in adults (see section 5.1):

- Complicated intra-abdominal infections (see section 4.4);
- Acute pyelonephritis;
- Complicated urinary tract infections (see section 4.4).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that ceftolozane (sulfate) contained in the medicinal product Zerbaxa, is qualified as a new active substance.