



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation
Report for ceftolozane (as sulfate) /
tazobactam (as sodium salt)

Proprietary Product Name: Zerbaxa

Sponsor: Merck Sharp & Dohme Australia Pty
Ltd

First round CER: March 2015

Second round CER: July 2015

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List of abbreviations

| Abbreviation | Meaning |
|--------------------|---|
| %T>MIC | Time as percentage of the dosing interval that the total drug concentration exceeds the MIC |
| AE | Adverse Event |
| AIC | Akaike's information criteria |
| ALB | Albumin |
| ALBn | Normalised albumin |
| ALP | Alkaline phosphatase |
| ALPn | Normalised alkaline phosphatase |
| ALT | Alanine transaminase |
| ALT (SGPT) | Alanine aminotransferase |
| AST | Aspartate transaminase |
| AST (SGOT) | Aspartate aminotransferase |
| ATC | Anatomic Therapeutic Classification |
| ATV | atazanavir |
| AUC _{0-t} | Area under the concentration versus time curve from 0 to end of the dosing interval |
| BAL | Bronchoalveolar Lavage |
| BIC | Bayesian Information Criteria |
| BILI | Total bilirubin |
| BLI | Beta-lactamase inhibitor |
| BLQ | Below the limit of quantification |
| BMI | Body mass index |
| BP | Blood pressure |
| bpm | Beats per minute |
| BUN | Blood Urea Nitrogen |

| Abbreviation | Meaning |
|------------------------|--|
| C ₀ | plasma concentration at time 0 |
| C ₂₄ | plasma concentration at 24 hours |
| CE | Clinically evaluable |
| CFR | Code of Federal Regulations |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| cIAI | Complicated intra-abdominal infection |
| Clast Plasma or ELF | concentration when last quantifiable concentration was observed |
| CL | Clearance |
| CLCR | Creatinine Clearance |
| cLUTI | complicated lower urinary tract infection |
| C _{max} | Maximum plasma and ELF concentration observed |
| CPK | Creatine nasep hosphoki |
| CrCl | Creatinine clearance |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| C _{trough} | Concentration of free drug at the end of the first cycle |
| cUTI | Complicated urinary tract infection |
| CV | Coefficient of Variation |
| CWRES | Weighted Residuals evaluated at individual conditional estimates |
| CXA-201 | Investigational Drug, CXA-101/tazobactam |
| DV | Dependent variable |
| EC ₅₀ | Plasma concentration at 50% maximal effect |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |

| Abbreviation | Meaning |
|------------------|---|
| EDC | Electronic Data Capture |
| ELF | Epithelial Lining Fluid |
| ELISA | Enzyme Linked ImmunoSorbent Assay |
| EMA | European Medicines Agency |
| E _{max} | Maximum effect |
| EOT | End-of-Therapy |
| ESBL | Extended-Spectrum β Lactamase |
| ET | Early termination |
| ETA | Random effect describing the deviation of the individual empirical Bayes estimate of the parameter from the typical population parameter estimate |
| F | bioavailability |
| F _{rel} | relative bioavailability |
| FDA | Food and Drug Administration |
| FEV1 | Forced Expiratory Volume in 1 second |
| FOCE | First order conditional estimation |
| GCP | Good Clinical Practice |
| GOF | Goodness of fit plots |
| i.v. / IV | intravenous |
| IAI | intra-abdominal infection |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| INR | International normalized ratio |
| INTER | Interaction |
| IOV | Inter-occasion variability |

| Abbreviation | Meaning |
|--------------|---|
| IPRED | Model predictions for the individual subject |
| IRB | Institutional Review Board |
| IRES | Residuals based on individual prediction |
| IIV | Inter-Individual variability |
| IV | Intravenous |
| IWRES | Weighted residuals based on individual prediction |
| HIV | human immunodeficiency virus |
| HT | Height |
| k_{el} | Elimination rate constant |
| k_{int} | Bound drug internalization rate constant |
| k_m | Concentration of drug corresponding to half of maximum binding capacity |
| k_{pt} | Plasma to tissue rate constant |
| k_{tp} | Tissue to plasma rate constant |
| LFU | Late follow-up |
| LLN | Lower limit of normal |
| LLOQ | Lower limit of quantification |
| LOCF | last observation carried forwards |
| LOQ | Limit of quantification |
| ME | Microbiologically evaluable |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIC | Minimum inhibitory concentration |
| MIC90 | Minimum inhibitory concentration required to inhibit the growth of 90% of organisms |
| MITT | Modified intent-to-treat |
| mmHg | Millimeter of mercury |

| Abbreviation | Meaning |
|--------------|--|
| mMITT | Microbiological modified intent-to-treat |
| NM-TRAN | NONMEM translator |
| NONMEM | Nonlinear mixed effects model |
| NPDE | Normalized Prediction Distribution Errors |
| PBP | Penicillin-binding proteins |
| PBP3 | Penicillin-binding protein 3 |
| PCS | Potentially clinically significant |
| PD | Pharmacodynamic |
| PI | Product Information |
| PK | Pharmacokinetic |
| PK/PD | Pharmacokinetics/pharmacodynamics |
| PRED | Predicted Data based on population parameter estimates |
| PREDPP | Prediction for population pharmacokinetics |
| PT | Prothrombin time |
| PTA | Probability of target attainment |
| Q | Inter-compartmental clearance |
| QQ | Quantile-quantile |
| q12h | Every 12 hours |
| q6h | Every 6 hours |
| q8h | Every 8 hours |
| RBC | Red blood cell |
| RES | Residuals based on population prediction |
| RSE | Relative standard error |
| RTV | ritonavir |
| SAE | Serious Adverse Event |

| Abbreviation | Meaning |
|--------------------|---|
| SAEM | Stochastic Approximation Expectation Maximization |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| spp | Species |
| $t_{1/2\lambda 1}$ | Distribution half-life for free drug |
| $t_{1/2\lambda z}$ | Terminal half-life for free drug |
| TAD | Time After Dose |
| TEAE | Treatment-emergent Adverse Event |
| Tlast | Time when the last quantifiable concentration was observed |
| Tmax | Sampling time at which Cmax occurred |
| tmax | Time to reach maximum concentration (end of infusion) |
| TP | Total protein |
| TPn | Normalised total protein |
| TOC | Test-of-cure |
| ULN | Upper limit of normal |
| UTI | urinary tract infection |
| V1 | Distribution volume for central compartment of free drug |
| V2 | Distribution volume for peripheral compartment of free drug |
| V3 | Distribution volume of bound drug (Vb) |
| Vb | Volume of distribution of bound drug |
| VEGF | Vascular Endothelial Growth Factor |
| Vmax | Maximum binding capacity |
| Vp | Central volume of distribution of free drug (L) |
| Vt | Peripheral volume of distribution of free drug |

| Abbreviation | Meaning |
|---------------|--|
| VSS | Steady state volume of distribution |
| WAM | Wald's approximation method |
| WBC | White blood cell |
| WHO | World Health Organization |
| WRES | Weighted residuals |
| WT | Weight |
| ε | Residual random effect |
| η | Inter-individual random effect |
| θ | Population mean value of the parameter |
| κ | Inter-occasion random effect |
| σ^2 | Variance of ε |
| φ^2 | Variance of κ |

Glossary of terms

| Abbreviation | Meaning |
|--------------|--|
| FO | First Order estimation method in NONMEM. NONMEM is a parametric maximum likelihood method. The likelihood of the observations, given model parameters and input variables, is the product of all individual likelihoods expressed as an integral over all possible values of ETA. Most often, no closed form solution of the integral exists for nonlinear mixed-effects models, thus necessitating an approximation of the expression being integrated. The FO method is based on the first order Taylor series approximation to the model, with the model linearised about the mean of the random parameters (at the expected value of etas, which is 0, i.e. at the typical value). For residual error models with dependency on model predictions (heteroscedastic models), the prediction corresponds to the population prediction. |
| FOCE | First Order Conditional Estimation method in NONMEM. In this method the model is linearised about the individual conditional estimates of etas (at the empirical Bayes estimates of eta, i.e. at the individual value). For residual error models with dependency on model predictions (heteroscedastic models), the prediction corresponds to the population prediction. |
| INTER | First Order Conditional Estimation method (see FOCE) with interaction in NONMEM. As FOCE with the following difference: For residual error models with dependency on model predictions (heteroscedastic models), the prediction corresponds to the individual prediction, i.e. the interaction between inter-individual variability and residual error is taken into account. |
| LRT | Likelihood Ratio Test. Test for statistical significance. The difference in -2LL between two nested models approximately follows a chi squared distribution, where the degrees of freedom is the difference in the number of estimated parameters. |
| OFV | Objective Function Value, approximately proportional to minus twice the log-likelihood (-2LL) |

1. Introduction

This is a submission to register a new chemical entity, Zerbaxa, as a fixed combination medicinal product. In this fixed combination product, the component of ceftolozane sulphate is a new chemical entity while the component of tazobactam sodium is currently registered in Australia as a component of Tazocin (piperacillin/tazobactam).

2. Clinical rationale

Complicated urinary tract infection (UTI) is a heterogeneous clinical entity that includes UTI in the presence of factors that predispose to persistent or relapsing infection (e.g. indwelling catheters, urinary obstruction, instrumentation of the urinary tract), and pyelonephritis. According to the sponsor, complicated UTIs (cUTIs) 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, with the most common uropathogens being *Escherichia coli* (*E. coli*), *Klebsiella* spp, *Pseudomonas* spp, *Proteus* spp, *Enterobacter* spp, and *Citrobacter* spp.

Complicated intra-abdominal infection (IAI) includes a wide variety of infections ranging from appendiceal abscesses to more severe conditions such as intestinal perforation with diffuse faecal peritonitis. These infections are associated with significant morbidity and mortality when inadequately treated or when accompanied by septic shock. According to the sponsor, although the bacteriology of complicated IAI (cIAI) depends on the anatomic origin of the infection, these infections are usually polymicrobial and involve a wide variety of Gram-positive and Gram-negative aerobic and anaerobic organisms. Pathogens most commonly encountered in cIAI are *E. coli*, other common Enterobacteriaceae, *Pseudomonas aeruginosa* (*P. aeruginosa*), and anaerobes (e.g. *Bacteroides fragilis*).

Although multiple antimicrobial agents are approved for use in cUTI and cIAI, the emergence of resistance to these agents (e.g. fluoroquinolone-resistant and extended-spectrum beta-lactamases [ESBL]-producing Enterobacteriaceae) has created an unmet medical need. The sponsor is of the opinion that there is a need for new antimicrobial agents with stability to common resistance mechanisms, especially the ESBLs of *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*), and those occurring in *P. aeruginosa*. Based on this rationale, the sponsor developed Zerbaxa, composed of ceftolozane, a novel cephalosporin with potent anti-pseudomonal activity, and tazobactam, an established BLI. The BLI activity of tazobactam is expected to protect ceftolozane from the majority of common ESBL-producing Enterobacteriaceae.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 13 clinical pharmacology studies, including 12 that provided pharmacokinetic data and 1 that provided pharmacodynamic data.
- 4 population pharmacokinetic analyses
- 6 population pharmacokinetic / pharmacodynamics analyses

- 2 pivotal efficacy/safety study reports (CXA-cUTI-10-04-05 [pooled analyses of studies CXA-cUTI-10-04 and CXA-cUTI-10-05] and CXA-cIAI-10-08-09 [pooled analyses of studies CXA-cIAI-10-08 and CXA-cIAI-10-09])

3.2. Paediatric data

The submission did not include paediatric data. The sponsor had stated that Zerbaxa is currently proposed only for use in adults. A deferral of paediatric studies has been granted in the US until post-marketing safety data is available in the adult population and paediatric data is not required to be submitted in the US and EU until December 2016.

3.3. Good clinical practice

The pivotal clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies.

| PK topic | Subtopic | Study ID |
|---------------------------------------|--|---|
| PK in healthy adults | General PK - Single dose | CALI-RAS-001 |
| | | CUBI-RAS-006 CXA-101-01 CXA-201-01 CXA-ELF-10-03 |
| | - Multi-dose | CXA-MD-11-07 |
| | Bioequivalence† - Single dose | No studies |
| | - Multi-dose | No studies |
| | Food effect | No studies |
| | PK in special populations | Target population § - Single dose |
| - Multi-dose | | CXA-101-03 |
| Hepatic impairment | | |
| Renal impairment | | CXA-201-01 CXA-101-02 CXA-201-02 CXA-REN-11-01 |
| Neonates/infants/children/adolescents | | Not studies |
| Elderly | | No studies |
| Other special population | | none |
| Genetic/gender-related PK | Males vs. females | Population PK |
| PK interactions | Caffeine, midazolam, furosemide | CXA-DDI-12-10 |
| Population PK analyses | Healthy subjects | CXA-PH-001 |
| | Target population | |
| | Volunteers and patients Impaired and normal renal function End Stage Renal Disease | CUBI-PCS-100 CXA-PH-002 CXA-POPPK-002 |

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

Ceftolozane, as a single agent, was investigated in two Phase 1 studies. A total of 60 subjects in these studies were exposed to ceftolozane single doses up to 2 g and multiple doses up to 3 g daily for up to 10 days. Ceftolozane/tazobactam was investigated in 7 Phase 1 studies. A total of 198 subjects in these studies were exposed to ceftolozane/tazobactam single doses up to 4.5 g and multiple doses up to 3 g daily for up to 10 days. Two Phase 2 studies, including 1 in subjects with complicated urinary tract infection (cUTI) and 1 in subjects with complicated intra-abdominal infection (cIAI), included PK assessments.

The PK of ceftolozane/tazobactam is linear and independent of treatment duration, with single-dose PK predictive of that after multiple-dose administration every 8 hours. Low plasma protein binding, minimal metabolism, and V_{ss} comparable to extracellular fluid suggest penetration of free, pharmacologically active ceftolozane/tazobactam into tissues. In addition, the predominantly renal route of elimination results in significantly higher renal concentrations (>20-fold those of plasma C_{max} for 50% of the dosing interval) making this compound well suited for the treatment of cUTIs. Dose adjustment is recommended in moderate or severe renal impairment (reduced by 2-fold or 4-fold, respectively), as well as in patients with ESRD on HD, but no dose adjustment is warranted based on any other subject covariates, including mild renal impairment, age, gender, body weight, or race. The predictable and linear PK, minimal DDI potential, accumulated safety data with doses up to 3 g every 8 hours, and the probability of target attainment (PTA) estimated from population PK/PD assessments, support the selection of the ceftolozane/tazobactam 1.5 g every 8 hours dosing regimen in patients with normal renal function or mild renal impairment.

4.2.1. Physicochemical characteristics of the active substance

The following information is derived from the Sponsor's summaries in Module 2. 7.1

Ceftolozane sulphate (ceftolozane) is a semisynthetic, parenteral antibiotic of the cephalosporin class. Ceftolozane has a molecular formula of $C_{23}H_{31}N_{12}O_8S_2 \cdot HSO_4$ and the molecular weight is 764.77. The chemical name is:

1H-Pyrazolium,5-amino-4-[[[(2-aminoethyl)amino]carbonyl]amino]-2-[[[(6*R*,7*R*)-7-[[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-,sulfate (1:1)

Ceftolozane is a white to off-white powder. Solubility of ceftolozane at 25°C is approximately 27.0 mg/mL in water, 35.0 mg/mL in 0.05 M sodium perchlorate at pH 2.5, and 32.3 mg/mL in 0.05 M sodium perchlorate at pH 4. Ceftolozane is insoluble in isopropanol, acetonitrile, dichloromethane, and meth-*tert*-butyl ether; and slightly soluble in *N*-methyl-pyrrolidine. Ceftolozane decomposes at approximately 170°C without melting. The mono-sulphate salt is hygroscopic, and the water content increases at various humidity conditions.

Tazobactam acid is a penicillanic acid sulfone derivative. Tazobactam has a molecular formula of $C_{10}H_{11}N_4NaO_5S$ and molecular weight is 322.28 g/mol (for sodium salt). The chemical name is:

Sodium (2*S*,3*S*,5*R*)-3-methyl-7-oxy-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate-4,4-dioxide

Tazobactam is a white to off-white powder. It is highly soluble in water. The melting point is >170°C.

Ceftolozane sulphate/tazobactam sodium (Zerbaxa) is a white to yellow powder for solution. After reconstitution with 10 ml diluent, the concentrations are 100 mg/ml ceftolozane equivalent and 50 mg/ml tazobactam equivalent. Zerbaxa solutions range from clear, colourless solutions to solutions that are clear and slightly yellow.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Not relevant as the drug is to be administered intravenously

4.2.2.2. Bioavailability

Not applicable as all studies used an intravenous formulation.

4.2.2.2.1. Bioequivalence of clinical trial and market formulations

Not applicable.

4.2.2.2.2. Influence of food

None conducted as the drug combination is to be used an intravenous formulation.

4.2.2.2.3. Dose proportionality

Ceftolozane exhibited dose proportional and linear PK over a wide range of doses from 250 mg to 3 g. The dose-normalised plasma concentration-time profiles for the various dose groups were superimposable (Study CXA-101-01). Given the relatively short $t_{1/2}$, ceftolozane did not accumulate and steady-state appeared to be achieved rapidly at the end of Day 3, the first sampled time point after multiple dose administration.

Dose proportionality was further assessed in study CXA-QT-10-02, which was conducted in healthy volunteers, using a one-way repeated measures ANOVA model on the natural logarithm (ln)-transformed AUClast/dose, AUC_{∞} /dose, and C_{max} /dose from the therapeutic and supra-therapeutic doses. The percent ratio of least squares means was ~100% and 90% CIs of ceftolozane PK parameters (AUClast/dose, AUC_{∞} /dose, and C_{max} /dose) were within the 80% to 125% range. These results indicate that the PK of ceftolozane was linear when ceftolozane doses were increased from 1 to 3 g.

Tazobactam dose proportionality was assessed in Study CXA-QT-10-02 which was conducted in healthy volunteers, using a one-way repeated measures ANOVA model on the ln-transformed AUClast/dose, AUC_{∞} /dose, and C_{max} /dose from the therapeutic and supra-therapeutic doses. The ratio of least squares means and 90% CIs of tazobactam PK parameters (AUClast/dose, AUC_{∞} /dose, and C_{max} /dose) were all within the 80% to 125% range, indicating that tazobactam PK from ceftolozane/tazobactam was linear when tazobactam doses were increased from 500 mg to 1.5 g. The results from other studies (CXA-201-01) were also consistent with tazobactam exposure increasing in an apparent dose-proportional manner.

4.2.2.2.4. Bioavailability during multiple-dosing

Not relevant.

4.2.2.2.5. Effect of administration timing

No studies were provided.

4.2.2.3. Distribution

4.2.2.3.1. Volume of distribution

Ceftolozane/tazobactam V_{ss} in healthy subjects was independent of dose, exceeding plasma volume indicating distribution of ceftolozane/tazobactam to the extravascular space. Intra-

Table 2: Submitted pharmacodynamic studies.

| PD Topic | Subtopic | Study ID |
|---|---|--|
| Primary Pharmacology | Effect on clinical and microbiological response | CUBI-RAS-008 |
| Secondary Pharmacology | Effect on QTc Interval | CXA-QT-10-02 |
| Gender other genetic and Age-Related Differences in PD Response | Effect of gender | Not conducted |
| | Effect of age | Not conducted |
| PD Interactions | | Not conducted |
| Population PD and PK-PD analyses | Healthy subjects | CXA-101-PH-003 |
| | Target population | CXA-101-PH-003 CUBI-RAS-003 ICPD 00319 ICPD 00319-2 |

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

The efficacy of 1 g ceftolozane alone (subjects with cUTI) or with 500 mg tazobactam (subjects with cIAI), both given every 8 hours as an IV 1-hour infusion, were studied in two Phase 2 studies. Primary endpoint in these studies was microbiological eradication rate at the test of cure (TOC) visit. Secondary efficacy was the per-subject clinical response rate at the TOC. In both studies, ceftolozane alone or ceftolozane/tazobactam were shown to be similarly effective to the control regimen for the primary and key secondary efficacy endpoints. The relationship between exposure and efficacy or safety was assessed based on the data from the Phase 2 cUTI and cIAI trials. A dose of 1.5 g ceftolozane/tazobactam was associated with a limited number of clinical failures, suggesting that adequate exposures were achieved.

A thorough QTc study examined the effect of single doses of ceftolozane / tazobactam on the change from baseline in the ECG in healthy volunteers. QTc interval was calculated using the Fridericia's and Bazett's method. There was an absence of clinically relevant effects of a therapeutic and 3-fold supra-therapeutic dose of ceftolozane / tazobactam (3g / 1.5g) on ECG parameters, including the QTc interval. Moxifloxacin (400mg) was included as a positive control.

5.2.1. Mechanism of action

Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs), resulting in inhibition of cell-wall synthesis and subsequent cell death. Ceftolozane has a high affinity to *Pseudomonas aeruginosa* PBPs [PBP1b (IC₅₀ 0.07 mg/L), PBP1c (IC₅₀ 0.64 mg/L), PBP2 (IC₅₀ 1.36 mg/L), PBP3 (IC₅₀ 0.02 mg/L) and PBP4 (IC₅₀ 0.29 mg/L)] and *Escherichia coli* PBP3 (IC₅₀ 0.03 mg/L) (M2.6.2.2.1.1).

Tazobactam, a beta-lactam structurally related to penicillins, is a potent, irreversible inhibitor of Class A broad-spectrum and extended-spectrum beta-lactamases and Class C cephalosporinases, which commonly cause resistance to penicillins and cephalosporins. Tazobactam extends the antimicrobial spectrum of ceftolozane to include beta-lactamase-producing bacteria.

Ceftolozane/tazobactam is a potent antibiotic with a spectrum of activity that includes clinically relevant Gram-negative pathogens including members of the Enterobacteriaceae such as *E. coli* and *K. pneumoniae*, non-fermenters such as *P. aeruginosa*, Gram-positive pathogens such as *S. pneumoniae* and *S. pyogenes* and anaerobic pathogens such as *B. fragilis*.

Ceftolozane/tazobactam has activity against strains of *P. aeruginosa* that are resistant to carbapenems, cephalosporins, fluoroquinolones and/or aminoglycosides, including many multiple drug resistant (MDR) isolates. Surveillance studies of ceftolozane and ceftolozane/tazobactam were performed in laboratories in the United States (US) (CXA201-M-003, CXA-022-MC, CXA-048-MC) Canada (CXA-018-MC, CXA-075-MC) and the European Union (EU) (CXA-017-MC, CXA-054-MC). More than 33,000 contemporary (2008-2012) clinical isolates were tested for ceftolozane/tazobactam susceptibility using a fixed concentration of tazobactam (4µg/mL). Non-duplicate isolates were collected from patients with serious infections including bloodstream infections, acute bacterial skin and skin structure infections and respiratory tract infections in hospitalized patients. MIC values were determined using standard broth micro-dilution or agar dilution methods according to established guidelines for 2011 and 2012 US and EU surveillance data.

The MIC₉₀ for ceftolozane/tazobactam against a wide array of *P. aeruginosa* strains (MIC₉₀ 0.5/4µg/mL) is the lowest among all systemically administered anti-pseudomonal antibiotics, except for colistin. Ceftolozane/tazobactam is active against the majority of Enterobacteriaceae. The MIC_{50/90} for *E. coli* is 0.25/0.5µg/mL and for *E. coli* strains with an ESBL phenotype the MIC_{50/90} is 0.5/4µg/mL. Study CXA.049.MC is a comprehensive report which summarises the activity of ceftolozane/tazobactam and comparators against the most frequently isolated strains from the EU and US surveillance and clinical studies (CXA201-M-003, CXA.017.MC, CXA.018.MC, CXA.022.MC, CXA.048.MC, CXA.054.MC, CXA.075.MC). Data was also presented which describes the activity of ceftolozane/tazobactam against multi-drug resistant *E. coli*, *K. pneumoniae* and *P. aeruginosa* which was generated as a subset of data from the large scale surveillance data. Activity against anaerobic species, Gram-positive organisms, ceftazidime resistant and susceptible organisms and non-fermentative Gram-negative bacilli are included. Finally, ceftolozane/tazobactam MIC distributions generated using combined 2008, 2011 and 2012 surveillance data against the most frequently encountered pathogens in surveillance are contained in this study report. Additionally, an additional study of over 400 isolates from Australia was conducted evaluating the activity of ceftolozane and comparator antibiotics against pathogens isolated in Australia in 2013 (CXA.092.MC). Compared to the comparator antimicrobial agents tested, ceftolozane/Tazobactam demonstrated the highest overall and spectrum of activity against contemporary (2013) Australian Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* spp.

Single and multiple *in vitro* passage studies as well as 10-day hollow-fibre models indicate a low potential for development of resistance in *Pseudomonas aeruginosa* and ESBL-positive *Escherichia coli* (2.6.2.2.1). In *P. aeruginosa*, ceftolozane is also stable to hydrolysis by AmpC

because of its low affinity for the AmpC enzyme. Additionally, ceftolozane is not affected by loss of outer membrane protein D (OprD) and is not a substrate for active efflux (2.6.2.2.3 -2.6.2.2.4).

Ceftolozane/tazobactam was shown to be less likely than piperacillin/tazobactam or ceftazidime to be affected by the development of mutational resistance (CXA.031.MC, CXA.084.MC, CXA.072.MC). However, in AmpC-producing isolates, ceftolozane/tazobactam selected for higher resistance rates compared to cefepime; in contrast, ceftolozane/tazobactam selected for less resistance than cefepime in ESBL-producing isolates.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The PD effect of ceftolozane / tazobactam was evaluated in study CXA-IAI-10-01 while the PK data from the study were available in CUBI-RAS-008. The primary objective was to determine the clinical response of ceftolozane / tazobactam plus metronidazole vs. meropenem in the treatment of hospitalized subjects with complicated intra-abdominal infections (cIAI) at the test of cure (TOC) visit (7 to 14 days after the completion of study drug administration). A secondary objective was to compare the microbiological response of both regimens at the TOC visit. The study was a prospective, randomized, double-blind evaluation of 60-minute IV infusions of ceftolozane / tazobactam (1000/500 mg q8h) and metronidazole (500 mg q8h) versus meropenem (1000 mg q8h) IV and a matching saline placebo (q8h) in male and female adult subjects with complicated intra-abdominal infections. Clinical response at the TOC visit are summarised in Table 3. The clinical cure rates at TOC in the mMITT population were 83.6% and 96.0% in the ceftolozane / tazobactam and meropenem groups, respectively, and in the ME population were 88.7% and 95.8%, respectively. Although the cure rates for the ceftolozane / tazobactam group were lower than those observed with meropenem, the 95% confidence intervals around the cure rates were wide and overlapping for the 2 therapies in both analysis sets. Microbiological success at TOC in the ME population was observed in 90.6% and 95.8% of subjects in the ceftolozane / tazobactam and meropenem groups. Clinical relapse was uncommon in both treatment groups (3.1%) and no subjects experienced microbiological recurrence at the long term follow-up visit.

Table 3: Clinical Response at the Test of Cure Visit (mMITT and ME Populations).

| Clinical Response, TOC | mMITT Population | | ME Population | |
|------------------------------|----------------------------------|---------------------|----------------------------------|---------------------|
| | 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

mMITT Microbiological Modified Intent-to-Treat

ME Microbiologically evaluable

The PD effect of ceftolozane was evaluated in study CXA-101-03. The study compared the efficacy of intravenous (IV) ceftolozane (1000 mg every 8 hours [q8h]) versus IV ceftazidime (1000 mg q8h) for 7 to 10 days in hospitalized adult subjects with cUTI including pyelonephritis. The primary objective was to determine the microbiological response at 6 to 9 days in subjects with complicated urinary tract infection (cUTI) during the 7- to 10-day treatment regimen. A secondary objective was to determine the clinical response at 6 to 9 days. Both study drugs were comparably effective in achieving high microbiologic cure rates across the different analysis populations. In the mMITT population, microbiologic cure rates at TOC were 83.1% and 76.3% in the ceftolozane and ceftazidime groups, respectively, and in the ME

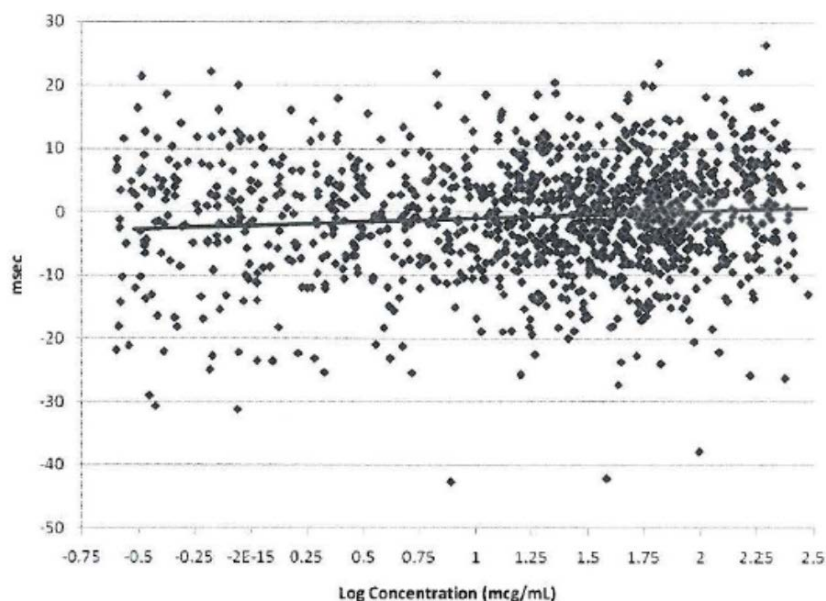
population were 85.5% and 92.6%, respectively. Microbiological cure rates among subjects with cLUTI were lower than in subjects with pyelonephritis but were comparable between the treatment groups. In the mMITT population, microbiological cure rates at TOC were 81.8% and 73.1% in the ceftolozane and ceftazidime groups, respectively, for subjects with cLUTI, and 85.7% and 83.3%, respectively, for subjects with pyelonephritis. Both study drugs showed activity against *E. coli* with eradication rates at TOC of 91.7% in the ceftolozane group and 94.7% in the ceftazidime group. As with microbiological response, both study drugs were comparably effective at achieving high clinical response rates at TOC: 90.8% and 92.1% in the ceftolozane and ceftazidime groups, respectively, in the mMITT population, and 92.7% and 100%, respectively, in the ME population. The sustained clinical cure rates at the long term follow-up visit were 98.0% for CXA-101 and 92.6% for ceftazidime. Microbiological recurrence was uncommon,

5.2.2.2. Secondary pharmacodynamic effects

5.2.2.2.1. Thorough QTc Study

A randomised, double-blind, double-dummy, placebo and active controlled, four-way crossover study that evaluated a single therapeutic (1000/500 mg) and a single supra-therapeutic (3000/1500 mg) IV dose of ceftolozane/tazobactam compared with placebo (CXA-QT-10-02). Moxifloxacin 400mg orally was used as a positive control to validate study sensitivity. All subjects received study drug on 4 dosing days (Days 1, 5, 9 and 13) with a 3-day wash-out period between doses. Single doses of ceftolozane/tazobactam did not increase QTc intervals in healthy volunteers. The largest mean difference from placebo for changes from pre-dose in QTcI ($\Delta\Delta\text{QTcI}$) was 4.16msec observed 1 hour following dosing with 3000/1500mg, and the largest one-sided 95% upper confidence bound was 6.25msec. Similar results were seen for $\Delta\Delta\text{QTcF}$ and $\Delta\Delta\text{QTcB}$; all upper 95% confidence bounds were <10msec. The 95% lower CIs on the differences from baseline for $\Delta\Delta\text{QTcI}$ between moxifloxacin and placebo at 2, 3 and 3.5 hour post dose were all >5msec and the time course of the moxifloxacin response indicated study sensitivity. No subjects had a QTc interval >480msec and the number of subjects with individual QTc intervals >450msec and increases in QTc from baseline > 30msec following dosing with ceftolozane/tazobactam were similar to placebo. No differential effects in mean differences from placebo in QTcI were seen between males and females. Results of the concentration-QTc response analysis supported the lack of effect of ceftolozane/tazobactam on the QTc interval (Figure 1). The estimated placebo-subtracted QTcI changes at all concentrations were small with all upper bounds of the one-sided 95% CI <5msec.

Figure 1: Time-Matched Differences From Placebo in Changes from Pre-dose Baseline QTcI Versus Log CEF Concentration.



Mean changes from baseline and outlier analyses for QRS and PR intervals also were similar following dosing with ceftolozane/tazobactam and with placebo and there were no ECG morphology changes suggesting a repolarization effect.

5.2.3. Time course of pharmacodynamic effects

Using an *in vitro* PD time-kill model, the killing kinetics of ceftolozane/tazobactam combinations was evaluated. A range of ceftolozane (1-256 μ g/mL) and tazobactam (1-64 μ g/mL) combinations were evaluated against four strains of *E. coli* (CXA-MC-039). Tazobactam had no activity against any of the strains when tested alone. Ceftolozane displayed time-dependent activity over the concentration range studied. The addition of tazobactam to ceftolozane increased the ceftolozane activity for all β -lactamase expressing strains. The concentration at which 50% of the maximal effect is achieved (EC_{50}) for ceftolozane was lowered in combination with tazobactam indicating increased potency with increasing tazobactam concentrations, reinforcing the concentration-dependent effect of tazobactam on ceftolozane activity.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

The PK and efficacy data from two Phase 2 (CXA-101-01; CXA-101-03) studies in subjects with cUTI and cIAI were used to evaluate exposure-response relationships. There was no clear trend across increasing exposure (AUC and C_{max}) with similar clinical and microbiological response rates observed across the 4 quartiles of exposure. Furthermore, there were very few failures across these studies, and in general the clinical failure rate observed was not associated with lower exposure.

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Not assessed.

5.2.6. Pharmacodynamic interactions

No pharmacodynamic drug interaction studies have been performed by the Sponsor with ceftolozane or tazobactam either alone or in combination.

5.2.7. Population PK-PD studies

A Monte Carlo (MC) simulation was used to evaluate the probability of PD target attainment for the optimal dosage regimen of ceftolozane in subjects with normal renal function based on the

MIC distributions of ceftolozane and ceftolozane / tazobactam for various pathogens from 2008 US surveillance study (CXA-101-PH-003). Isolates were randomly selected for the study so that they can represent current real antibiogram in US hospitals. The MICs of ceftolozane alone and ceftolozane/tazobactam (4 µg/mL) were determined for the following organisms: (1) *Streptococcus pneumoniae* (N=276), (2) *Streptococcus pyogenes* (N=42), (3) *Streptococcus agalactiae* (N=18), (4) *Pseudomonas aeruginosa* (N=914), (5) *Haemophilus influenzae* (N=95), (6) *Acinetobacter* species (N=238), (7) *Escherichia coli* (N=721), (8) *Klebsiella pneumoniae* (N=798), (9) *Enterobacter cloacae* (N=266), (10) *Citrobacter* species (N=158), (11) *Proteus mirabilis* (N=352), (12) *Serratia marcescens* (N=256), and (13) all Enterobacteriaceae (N=2551). The population PK model of ceftolozane was developed based on the PK data collected from study CXA-101-01. The MC simulation was performed using NONMEM to simulate steady-state ceftolozane plasma concentrations in subjects with normal renal function following 1g q8h multiple dosing. Using the 50% T>MIC as a target, ceftolozane and ceftolozane /tazobactam had excellent target attainment for species like Streptococci, Enterobacteriaceae, *H. influenzae* and *P. aeruginosa*. Ceftolozane and ceftolozane/tazobactam had excellent probability of target attainment for *P. aeruginosa*, even up to 70% of the dosing interval. The combination with tazobactam can improve the susceptibility of Enterobacteriaceae, especially for species like *E. coli*, *K. pneumoniae* and *Citrobacter* species.

Three similar population PK / PD models were performed to determine optimal dosing for the fixed-dose combination product ceftolozane/tazobactam.

Key exposure values of ceftolozane known to correlate with microbiological response (time-dependent parameter such as drug T>MIC) were derived to determine efficacy of the ceftolozane /tazobactam combination product, to ultimately support optimal dosing regime (CUBI-RAS-003). Based on Monte Carlo simulation pathogens with an MIC of up to 2 µg/mL, a 1-hour ceftolozane/tazobactam infusion of 1000/500 mg q8h would result in at least 96.7% target attainment, with little benefit expected from an increase in infusion duration to 3 hours, or from a doubling in dose. For pathogens with an MIC of 4µg/mL, a 1-hour ceftolozane /tazobactam infusion of 1000/500 mg q8h would result in a target attainment of 60% T>MIC of 95.5% of an 8-hour dosing interval. For target T>MIC of 60% or greater and MIC values of 8 or 16 µg/mL, prolonged 3-h infusion or higher doses can result in greater target attainment. Within the range of simulated dose regimens, low attainment rates (≤74.2% for 40% T>MIC or above) are expected to be achieved against pathogens with an MIC of 32 µg/mL or above. The predicted cumulative fraction of response is consistently above 99% against *P. aeruginosa*; exceeds 98% in *S. pneumoniae*; 93% in the Enterobacteriaceae family as a whole; 97% specifically in *E. coli*. In patients with either moderate or severe renal impairment, target attainment rates in excess of 90% could be achieved with a lower dose of 500/250 mg ceftolozane /tazobactam given every 8 hours.

The remaining two PK/PD studies also used Monte Carlo simulations to support recommendations for *in vitro* susceptibility test interpretive criteria for ceftolozane/tazobactam against *P. aeruginosa* (ICPD 00319) or *Enterobacteriaceae* (ICPD 00319-2) and to select ceftolozane/tazobactam dosing regimens by renal function category. As in the previous simulations, adequate antibacterial activity against these two micro-organisms should be achieved with a 1-hour ceftolozane/tazobactam infusion of 1000/500 mg q8h in patients with normal renal function. Dose reduction to 500/250 mg q8h in moderate renal impairment and to 250/125 mg q8h in severe renal impairment is predicted to achieve adequate control.

5.3. Evaluator's conclusions on pharmacodynamics

For ceftolozane/tazobactam, the most important PK/PD index correlating with *in vivo* efficacy is the duration that the plasma concentration remains above the drug's MIC for target Gram-negative pathogens, described as the percentage of the dosing interval (%T>MIC). An extensive

series of population PK/PD models, based on the PK data derived from Phase 1 studies and *in vitro* and *ex-vivo* antibacterial activity of ceftolozane/tazobactam, were undertaken to derive the doses necessary to achieve these responses. The derived clinically recommended dose of 1g/0.5g every 8 hours seems to have been established by these models. Two Phase 2 studies evaluated either the combination treatment or ceftolozane alone for efficacy in complicated intra-abdominal infections or complicated urinary tract infections. In both studies a 7-10day treatment gave >90% cure rates against the principal microbiological organisms *E. coli* and *P. aeruginosa*.

The evaluation of the combination treatment on the QTc interval was conducted in healthy volunteers. The study was adequately designed, included a positive control (moxifloxacin) and was conducted in a good sample size. The study evaluated single doses whereas the proposed clinical use is for repeated doses. The effect on the ECG in patients treated for therapeutic indications is therefore of further interest in addressing the cardiovascular effects of the combination.

6. Dosage selection for the pivotal studies

According to the sponsor, the PK/PD rationale for determining the clinical dosing of β -lactam antimicrobial/ β -lactamase inhibitor combination drugs is primarily based on the active β -lactam antibiotic component rather than on the combination of the β -lactam and β -lactamase inhibitor (BLI) components. The dose selection of tazobactam (the BLI component) for the pivotal studies was based on prior experience showing it to be well tolerated and efficacious in combination with piperacillin in Tazocin (piperacillin 4g/ tazobactam 500mg).¹ The dose selection of the ceftolozane component (the β -lactam antibiotic component) was largely based on its PK, PK/PD and safety profiles. PK studies showed that ceftolozane exhibited linear and time-independent PK and was well tolerated over a range of doses (250 mg to 3 g ceftolozane). Co-administration of ceftolozane and tazobactam did not change the PK profiles of ceftolozane or tazobactam.

In-vitro and *in-vivo* models of infections suggested that for the cephalosporin class of antibiotics, the PK/PD parameter that is most predictive of *in-vivo* efficacy is the duration that the drug plasma concentration remains above the drug's minimum inhibitory concentration (MIC) for target pathogens (i.e. percentage of the dosing interval that the total drug concentration exceeds the MIC; %T>MIC). The β -lactam antibiotics, including cephalosporins, are time-dependent bactericidal agents, and their antibacterial efficacy improves (up to a plateau) as the %T>MIC increases. The sponsor looked at the %T>MIC for various cephalosporin and pathogen combinations, which showed that %T>MIC values of free drug required for bacteriostatic effect with strains of Enterobacteriaceae and Streptococcus pneumoniae (*S. pneumoniae*) ranged from 35% to 41% with 4 third-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime, cefpirome). In selecting a dosing regimen for ceftolozane/tazobactam in the pivotal clinical studies, a 30%T>MIC was selected as a predictor of efficacy, based on findings that for ceftolozane/tazobactam, %T>MIC values of 26.3% and 31.6% achieved a bacteriostatic and 1-log kill effect, respectively, for 4 wild-type strains of Enterobacteriaceae, including *E. coli*, in the neutropenic mouse thigh infection model.

Monte Carlo simulations (N=1000 replicates) were conducted based on PK in subjects with normal and mild or moderate renal impairment and subjects with cUTI (including pyelonephritis) from a Phase 2 cUTI study (study CXA-101-03). The results showed that based on 30%T>MIC as predictor for efficacy, a 1.5g dose (1000 mg ceftolozane/500mg tazobactam) infused over 1 hour every 8 hours was predicted to produce sufficient drug concentrations to

¹ Current TGA approved recommended dosing regimen for Tazocin: IV infusion of piperacillin 4g/ tazobactam 500mg to be given 8 hourly.

cover target pathogens, including many β -lactam-resistant Enterobacteriaceae, and to provide adequate systemic drug exposures for the treatment of pyelonephritis or concurrent bacteraemia and for the treatment of cIAI.

Overall, the dose selection for the pivotal studies was in compliance with the TGA-adopted EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections² and the addendum to this guideline.³

7. Clinical efficacy

Pivotal data supporting the efficacy of ceftolozane/tazobactam in the treatment of cUTI and of cIAI were each derived from two Phase 3 studies with identical study design, incorporated into 1 pooled analysis per indication (cUTI: pooled analysis study report CXA-cUTI-10-04-05, derived from studies CXA-cUTI-10-04 and CXA-cUTI-10-05; cIAI: pooled analysis study report CXA-cIAI-10-08-09, derived from studies CXA-cIAI-10-08 and CXA-cIAI-10-09). The sponsor had requested scientific advice from the Committee for Medicinal Products for Human Use (CHMP) in December 2012 to discuss the potential to statistically pool the 2 cIAI and 2 cUTI studies into a single study per indication (decision to pool the data across the protocols was made prior to completion of the studies). According to the sponsor, the CHMP had agreed that pooling of the studies was possible and that analysis would have to be conducted at a 99% confidence interval with a 1-sided alpha level of 0.005 in accordance with the EMA guidelines.⁴ The US FDA had also agreed with the sponsor's pooling proposal.

The sponsor had provided the rationale for the pooling of data. As part of the original development programme for ceftolozane/tazobactam for the indications of use in cUTI and cIAI, the sponsor had initiated two identical Phase 3 cUTI protocols (CXA-cUTI-10-04 and CXA-cUTI-10-05), each with a planned sample size of 776 subjects, and two identical Phase 3 cIAI protocols (CXA-cIAI-10-08 and CXA-cIAI-10-09), each with a planned sample size of 906 subjects. Each study was multi-centre, multi-national, prospective, double-blind, active-controlled and randomised (stratified by investigational site for the cUTI studies, and by investigational site and primary site of infections for the cIAI studies). In September 2012, the FDA released a new draft Guidance for Industry for cIAI stipulating a single study pathway per indication for sponsors developing a drug for more than 1 indication caused by similar bacterial pathogens. The sponsor then obtained agreement from the CHMP and the FDA to proceed with a single-study strategy for the cUTI and cIAI indications, to be achieved by pooling data from the two identical Phase 3 cUTI protocols and the two identical Phase 3 cIAI protocols, providing one database per indication with appropriate total sample size and adequate power.

In accordance with statistical consideration in the EMA guidelines on "Points to consider on application with (1) meta-analysis; (2) one pivotal study", the total planned pooled sample size for the single cIAI analysis was revised to 988 subjects (494 subjects per treatment arm). This was projected to achieve the target sample size of 370 clinically evaluable subjects per treatment arm. Similarly, the total planned pooled sample size for the single cUTI analysis was revised to 954 subjects (477 subjects per treatment arm). This was projected to achieve the target sample size of 334 microbiologically evaluable subjects per treatment arm. In addition, for both indications the significance level was changed from 0.05 to 0.01 in accordance with the above-mentioned EMA guidance for a single study submission. The data from the individual

² European Medicines Agency, "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2)", 15 December 2011.

³ European Medicines Agency, "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013)", 24 October 2013.

⁴ European Medicines Agency, "Points to consider on application with (1) meta-analysis; (2) one pivotal study (CPMP/EWP/2330/99)", 31 May 2001.

protocols for each indication were pooled after database lock (prior to unblinding), analysed as one dataset, and are reported in one clinical study report per indication.

7.1. For the indication of treatment of complicated urinary tract infections, including pyelonephritis

7.1.1. Pivotal efficacy studies

7.1.1.1. Study Report CXA-cUTI-10-04-05

7.1.1.1.1. Study design, objectives, locations and dates

Studies CXA-cUTI-10-04 and CXA-cUTI-10-05 were multi-centre, randomised, double-dummy, double-blind, active-controlled studies comparing the safety and efficacy of intravenous ceftolozane/tazobactam and intravenous levofloxacin in complicated urinary tract infection (cUTI), including pyelonephritis. The primary objective was to demonstrate the non-inferiority of ceftolozane/tazobactam versus levofloxacin in adult subjects with cUTI (including pyelonephritis) based on the difference in microbiological response rate (ceftolozane/tazobactam minus levofloxacin) in the microbiologically evaluable (ME) population at the Test-of-Cure (TOC) visit (7 days [\pm 2 days] after last treatment) using a non-inferiority margin of -10%, at a 1-sided 0.005 significance level. The key secondary objective was to demonstrate the non-inferiority of ceftolozane/tazobactam versus levofloxacin in adult subjects with cUTI (including pyelonephritis) based on the difference in microbiological response rate (ceftolozane/tazobactam minus levofloxacin), in the microbiological modified intent-to-treat (mMITT) population at the TOC visit (7 days [\pm 2 days] after last treatment) using a non-inferiority margin of -10%, at a 1-sided 0.005 significance level.

Studies CXA-cUTI-10-04 and CXA-cUTI-10-05 were multi-centre studies involving in total 209 sites across the 2 studies (110 study sites in study CXA-cUTI-10-04 and 99 study sites in study CXA-cUTI-10-05). Of these, 135 sites in 25 countries enrolled at least 1 subject. Overall, 83 enrolling sites (61.5% of enrolling sites) were in 14 European countries⁵ and 40 enrolling sites (29.6% of enrolling sites) were in 9 European Union Member States.⁶ The study start dates (first subject enrolled) were 28 July 2011 and 15 September 2011 for studies CXA-cUTI-10-04 and CXA-cUTI-10-05, respectively. The study completion dates (last subject completed) were 4 September 2013 and 29 May 2013, respectively.

Eligible subjects were randomised (stratified by study site) in a 1:1 ratio to receive IV infusions of either ceftolozane/tazobactam (1.5g every 8 hours for 7 days)⁷ or levofloxacin (750mg once daily for 7 days). The study was blinded using double-dummy, saline infusions. Subject participation consisted of 3 phases: screening (baseline; Day -1 to Day 1), treatment (Day 1 to Day 7), and post-treatment which comprises of End-of-Therapy (EOT) visit (within 24 hours after the last dose of study drug), Test-of-Cure (TOC) visit (7 days [\pm 2 days] after the last dose of study drug), and Late follow-up (LFU) visit (28 to 35 days after the last dose of study drug). The first dose given on each day consisted of 2 infusions given simultaneously, 1 active drug and 1 dummy infusion. Subsequent infusions (active or dummy) were given every 8 hours. There were 4 daily infusions for each subject in each randomised treatment arm (3 active infusions and 1 dummy infusion in the ceftolozane/tazobactam arm; 1 active and 3 dummy infusions in the levofloxacin arm). Hospitalisation was mandatory during all IV study drug administration, with the exception of study sites that were approved for outpatient parenteral antibiotic therapy. In these cases, hospitalisation was mandatory during administration of at least the first 9 doses (approximately 3 days) of IV study therapy.

⁵ Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Ukraine

⁶ Bulgaria, Croatia, Estonia, Hungary, Latvia, Poland, Romania, Slovakia, Slovenia

⁷ "Ceftolozane/tazobactam 1.5g" refers to 1g ceftolozane/500mg tazobactam

7.1.1.1.2. Inclusion and exclusion criteria

Subjects enrolled in the study were adult (≥ 18 years of age) males (practising reliable birth control methods) or females (not of child-bearing potential or practising reliable birth control methods) with clinical signs and/or symptoms of cUTI (either pyelonephritis or complicated lower UTI [cLUTI] with a qualifying complication) and a urine microscopy demonstrating pyuria. In addition, eligible subjects had to have a pre-treatment baseline urine culture specimen collected within 24 hours before the start of administration of the first dose of study drug, and be judged to require IV antibacterial therapy for the treatment of the presumed cUTI.

Subjects were excluded if they had received any dose of a potentially therapeutic antibacterial agent for the treatment of the current UTI within 48 hours before the study-qualifying pre-treatment baseline urine was obtained. Subjects with intractable urinary infection at baseline that the investigator anticipated would require more than 7 days of study drug therapy, those with suspected or confirmed perinephric or intrarenal abscess, and those with suspected or confirmed prostatitis were also excluded.

Comments: The inclusion and exclusion criteria were appropriate and consistent with the TGA-adopted EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections⁸ and the addendum to this guideline,⁹ as well as the FDA Guidance for Industry on complicated urinary tract infections and pyelonephritis: developing antimicrobial drugs for treatment.¹⁰ The study definition of complicated UTI is consistent with clinical diagnosis. Overall, the study eligibility criteria looked to enrol subjects with cUTI (including pyelonephritis) who required parenteral antibiotic therapy.

7.1.1.1.3. Study treatments

Eligible subjects were randomised in a 1:1 ratio to receive IV infusions of either ceftolozane/tazobactam (1.5g every 8 hours) or IV levofloxacin (750mg once daily). Treatment duration was 7 days. Subjects undergoing urinary procedures (including removal of indwelling catheter, bladder instrumentation, and relief of obstruction) while on study therapy could receive up to 9 days of study treatment. Dose adjustments for renal insufficiency were performed by an unblinded pharmacist following notification from the investigator of the subject's creatinine clearance (CL_{CR}).¹¹ Subjects who developed severe renal failure ($CL_{CR} < 30$) were withdrawn from study drug administration because guidance for dose adjustment of ceftolozane/tazobactam in severe renal impairment was not available at the time the studies were conducted.

Comments: The study dose selection is appropriate. The dose selection for ceftolozane/tazobactam has been previously discussed. Overall, the choice and dose regimen of the active comparator, IV levofloxacin (a fluoroquinolone) 750mg once daily for 7 days is appropriate and consistent with clinical practice guidelines.¹² Levofloxacin, is not currently registered for use in Australia. A search with the European Medicines Agency (EMA) shows that levofloxacin is also not currently registered for use with the EMA, although levofloxacin as nebuliser solution (brand name of Quinsair) is under review for

⁸ European Medicines Agency, "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2)", 15 December 2011.

⁹ European Medicines Agency, "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013)", 24 October 2013.

¹⁰ Food and Drug Administration, Guidance for Industry: complicated urinary tract infections and pyelonephritis-developing antimicrobial drugs for treatment. February 2012.

¹¹ Dose adjustments based on renal function for ceftolozane/tazobactam: $CL_{CR} > 50$ mL/min and above- no dose adjustment required; $CL_{CR} 30-50$ mL/min- decrease dose to 750mg IV every 8 (± 2) hours (750mg ceftolozane/tazobactam = 500mg ceftolozane/250 mg tazobactam); $CL_{CR} < 30$ mL/min- discontinue study drug. Dose adjustments based on renal function for levofloxacin: $CL_{CR} > 50$ mL/min- no dose adjustment required; $CL_{CR} 30-50$ mL/min- decrease dose frequency to 750mg IV every 48 hours; $CL_{CR} < 30$ mL/min- discontinue study drug.

¹² European Association of Urology, Guidelines on urological infections. March 2013;

use in the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adult patients with cystic fibrosis. Levofloxacin (oral and intravenous formulations) is registered for use by the FDA in the US, and approved indications include the treatment of cUTI, including pyelonephritis. The dose of levofloxacin in this study (750mg once daily) is the highest approved dose for the treatment of cUTI (including pyelonephritis).¹³ The approved recommended dose for this indication is IV levofloxacin 750mg once daily for a duration of 5 days. The sponsor had acknowledged that the FDA-approved recommended dose for the indication of treatment of cUTI is 750mg daily for 5 days, but noted that the pivotal study leading to this indication for levofloxacin had been conducted several years ago (enrolment from November 2005 through April 2006) and that since then, global trends have shown increasing rates of fluoroquinolone resistance worldwide. As the ceftolozane/tazobactam clinical studies were conducted globally, the 750mg dose of levofloxacin was selected with an extended treatment duration of 7 days in order to account for the increasing rates of fluoroquinolone resistance. The 7-day treatment duration was also consistent with clinical guideline recommendations on the empirical treatment of cLUTI and pyelonephritis. In addition, the sponsor had noted that this dose and duration of levofloxacin had been widely used in the treatment of patients with nosocomial pneumonia for 7 to 14 days without major safety concerns.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy endpoint was the microbiological response rate at the TOC visit in the microbiologically evaluable (ME) population. The key secondary efficacy endpoint was the microbiological response rate at the TOC visit in the microbiological modified intent-to-treat (mMITT) population. Other secondary efficacy variables included the microbiological response rate at the EOT and LFU visits; clinical response rate of ceftolozane/tazobactam versus levofloxacin at the EOT, TOC, and LFU visits; incidence of superinfections and new infections; per pathogen microbiological eradication rates.

Each uropathogen found at baseline had a microbiological outcome at EOT and TOC visits. The by-subject microbiological response was determined prior to unblinding based on individual microbiological outcomes for each baseline uropathogen (if more than 1). For subjects with more than 1 uropathogen isolated at baseline, an overall outcome of microbiological eradication was based on eradication of all baseline uropathogens. If the outcome for any uropathogen was persistence, the subject was considered to have an overall microbiological response of persistence.

The microbiological eradication rate was the proportion of subjects in the relevant population who had an overall outcome of eradication. The per-pathogen microbiological outcome was also determined for each uropathogen isolated at baseline from a pre-treatment study-qualifying culture.

Subjects who were microbiological successes at the TOC visit (i.e. eradication of each of the uropathogens identified at baseline) had their microbiological outcome assessed at the LFU visit. As per the previous visits, the by-subject microbiological response at the LFU visit was based on individual outcomes for each baseline uropathogen. The sustained microbiological eradication rate was the proportion of subjects in the relevant population who had an overall outcome of sustained eradication. The per-pathogen microbiological outcome was also determined for each uropathogen isolated at baseline from a pre-treatment study-qualifying culture.

With regards to clinical response at the EOT and TOC visits, the investigator classified clinical response at these visits as clinical cure, clinical failure, or indeterminate based on clinical outcome definitions as summarised. A favourable clinical response was “clinical cure,” and the

¹³ US Prescribing Information for levofloxacin, September 2008.

clinical response rate was defined as the proportion of subjects in a relevant population with a response of clinical cure at the visit of interest (i.e. EOT or TOC). Subjects who were clinically cured at the TOC visit were reassessed at the LFU visit for evidence of sustained clinical cure or relapse of symptoms. The sustained clinical response rate was defined as the proportion of subjects in the relevant population with a response of sustained clinical cure at the LFU visit.

Comments: The primary and secondary endpoints are appropriate and consistent with the TGA-adopted EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections¹⁴ and the addendum to this guideline.¹⁵ Overall, the study primary and secondary endpoints allowed evaluations of microbiological and clinical effects after 7 days of treatment at 7 days after the last dose of study drug (TOC visit), at within 24 hours after the last dose of study drug (EOT visit), and at 28 to 35 days after the last dose of study drug (LFU visit).

7.1.1.1.5. Randomisation and blinding methods

Eligible subjects were randomised in a 1:1 ratio to receive IV infusions of either ceftolozane/tazobactam (1.5g) or levofloxacin (750mg). After informed consent was obtained and study eligibility was established, the study site pharmacist obtained, via the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS), the subject number and the study drug assignment from a centralised computer-generated randomisation schedule. Block randomisation, stratified by study site, was used to assign subjects to treatment groups. The studies were double-blind. Blinding was achieved using double-dummy, saline infusions.

7.1.1.1.6. Analysis populations

There were 8 analysis population sets in the study. The Intent-to-Treat (ITT) population was defined as 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 to which they were randomised. The Modified Intent-to-Treat (MITT) population consisted of all randomised subjects who received any amount of study drug. Subjects in the MITT population were also categorised based on the treatment to which they were randomised, irrespective of what they actually received. The Microbiological Modified Intent-to-Treat (mMITT) population was a subset of the MITT that included subjects who had at least 1 qualified uropathogen from a study-qualifying pre-treatment baseline urine specimen. The Clinically Evaluable at Test-of-Cure (CE at TOC) population was a subset of the mMITT population who adhered to study procedures and had a TOC visit within the specified visit window. All subjects in the CE at TOC population had to have an evaluable clinical outcome (i.e. an indeterminate response at the TOC visit was not acceptable for this population). The Microbiologically Evaluable at Test-of-Cure (ME at TOC) population was 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 result¹⁶ at the TOC visit. The Clinically Evaluable at Late Follow-Up (CE at LFU) population was a subset of the CE at TOC population and included all subjects who were clinical cures at the TOC visit, and had an LFU assessment (or were classified as a clinical failure after the TOC visit but prior to the LFU visit). An indeterminate clinical response at the LFU visit was not acceptable for this population. The Microbiologically Evaluable at Late Follow-Up (ME at LFU) population was a subset of the ME at TOC population and included all subjects who were microbiological successes at the TOC visit, and had an LFU assessment (or were classified as a microbiological failure after the TOC visit but prior to the LFU visit). An indeterminate clinical response at the LFU visit was not acceptable for this population. The Safety population

¹⁴ European Medicines Agency, "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2)", 15 December 2011.

¹⁵ European Medicines Agency, "Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013)", 24 October 2013.

¹⁶ An interpretable urine culture was defined as where the presence of a bacterial uropathogen could be clearly identified or excluded (i.e. the microbiological response was not indeterminate).

consisted of all subjects who received any amount of the study drug. Subjects in the Safety population were categorised based on the actual treatment that the subjects received, irrespective of the treatment to which they were randomised.

The primary and key secondary efficacy analyses were based on the ME at TOC and mMITT populations, respectively. The safety analyses were based on the Safety population.

Comments: The definitions of the analysis populations and the efficacy analyses on the ME at TOC and mMITT populations are in keeping with the TGA-adopted EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections¹⁷ and the addendum to this guideline.¹⁸ These guideline recommendations were generally similar to those in the FDA Guidance for Industry on complicated urinary tract infections and pyelonephritis: developing antimicrobial drugs for treatment,¹⁹ except that the FDA required the primary endpoint be the composite microbiological eradication and clinical response rate in the mMITT population, while the EMA guidances stated as acceptable the microbiological response rate in the per-protocol ME at TOC population. As previously described, the sponsor had stated that while the submission dossier for Australia is identical to the dossier submitted to the EMA, the clinical trial data in the US submission was presented differently to the EMA and Australian submissions, due to pre-submission discussions with the EMA, FDA and TGA on recommended/ acceptable primary and secondary endpoints and statistical analysis.

7.1.1.1.7. Sample size

It was estimated that a combined sample size of 954 subjects (477 subjects per arm) would be needed to provide approximately 334 microbiologically evaluable subjects per treatment arm (based on assumption that 70% of randomised subjects would meet the criteria to be included in the ME at TOC population). This would provide the combined study (i.e. pooled studies CXA-cUTI-10-04 and CXA-cUTI-10-05) with an overall power of approximately 80% to demonstrate non-inferiority of ceftolozane/tazobactam to levofloxacin at a 10% non-inferiority margin at a 1-sided alpha level of 0.005 in terms of the primary efficacy hypothesis. This sample size estimation was based on an assumed microbiological response rate of 82.8% for both groups at the TOC visit in the ME at TOC population.

7.1.1.1.8. Statistical methods

The primary and key secondary hypotheses were to establish non-inferiority of ceftolozane/tazobactam versus levofloxacin in the ME at TOC population and the mMITT population, respectively, based on the difference in the proportion of subjects who achieve microbiological eradication at the TOC visit. The hypotheses were tested at the 1-sided 0.005 significance level, through a 2-sided 99% confidence interval (CI) approach. The 2-sided 99% CI on the difference of ceftolozane/tazobactam minus comparator (levofloxacin) was constructed using stratified Newcombe CI with Minimum Risk weights. Non-inferiority was concluded if the lower bound of the 2-sided 99% CI was greater than -10.0% (non-inferiority margin), in the ME at TOC population and the mMITT population for the primary and key secondary efficacy endpoints, respectively. The randomisation in each of the individual protocols was stratified by investigation sites, but due to the large number of investigation sites and relatively small sample

¹⁷ European Medicines Agency, Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. 15 December 2011.

¹⁸ European Medicines Agency, Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. 24 October 2013.

¹⁹ Food and Drug Administration, Guidance for Industry: complicated urinary tract infections and pyelonephritis-developing antimicrobial drugs for treatment. February 2012.

size expected at each site, the primary analysis was adjusted with the stratification factor of region.²⁰

As a supportive analysis, an unstratified analysis with a 2-sided 95% Wilson Score CI for individual proportions and proportion difference (treatment – control) was also performed for the primary and key secondary efficacy endpoints. In addition, several sensitivity analyses (stratification by protocol and region, by baseline diagnosis, and by region excluding data from site 5609 with data integrity issues²¹) were performed for the primary and key secondary efficacy endpoints for overall assessment of the robustness of the results. Subgroup analyses (exploratory) were also performed on the primary and key secondary efficacy endpoints²².

For microbiological or clinical responses, missing or indeterminate responses were handled with a Data-as-Observed (DAO) approach for the ME at TOC population (i.e. missing or indeterminate responses were excluded) and a Treatment Failure Approach (TFA) for the mMITT population which was defined in the Statistical Analysis Plan (SAP) as: for the analyses of clinical response and microbiological response at the TOC visit in the mMITT population, subjects with a missing clinical response or microbiological response (e.g. indeterminate) would be categorised as treatment failures; a missing per-pathogen microbiological outcome at the TOC visit would be considered an indeterminate outcome unless the per-pathogen microbiological outcome at EOT was persistence (a per-pathogen microbiological outcome of persistence at EOT would be carried forward to the TOC visit) and likewise, a missing per-pathogen microbiological outcome at the LFU visit would be considered indeterminate unless the per-pathogen microbiological outcome at TOC was persistence; a missing clinical outcome at the TOC visit would be considered an indeterminate outcome unless the clinical outcome at EOT was failure (a clinical response of failure at EOT would be carried forward to the TOC visit).

Comments: The sponsor had not provided justification for the choice of inferiority margin of -10% in the clinical study report or the SAP. This will be raised as a clinical question for the sponsor. It is noted that the addendum to the EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections²³ states that the “suggested non-inferiority margin is -10%”. The FDA guidance²⁴ also states that “In most cases, a noninferiority margin of 10 percent will be clinically acceptable and scientifically justified. Sponsors should submit the justification for their choice of the noninferiority margin with phase 3 protocols”.

7.1.1.1.9. Participant flow

A total of 1083 subjects were enrolled and randomised: 543 to the ceftolozane/tazobactam group, and 540 to the levofloxacin group. Each study enrolled a similar number of subjects: 558 subjects in study CXA-cUTI-10-04 and 525 subjects in CXA-cUTI-10-05. A total of 1028 subjects

²⁰ Region was categorised as Eastern Europe (Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, Slovenia, and Ukraine), North America (Mexico and USA), Rest of World (India, Israel, South Africa, South Korea, and Thailand), South America (Brazil, Chile, Colombia, and Peru) and Western Europe (Germany and Spain).

²¹ A finding of GCP non-compliance with potential risk for data integrity was reported in a sponsor audit, conducted after the enrolment had closed, at site number 5609 (N=6 subjects [3 in each treatment group]).

²² Subgroups: baseline diagnosis (pyelonephritis vs. cLUTI); subjects with levofloxacin-resistant baseline uropathogens vs. subjects with levofloxacin-susceptible baseline uropathogens; CL_{CR} (≤50 mL/min vs. >50 mL/min); region (Eastern Europe vs. North America vs. Rest of World vs. South America vs. Western Europe); bacteraemia at baseline (yes vs. no); age categories (≥18 to <65 years vs. ≥65 to <75 years vs. ≥75 years) and (≥18 to <45 years vs. ≥45 to <65 years vs. ≥65 years).

²³ European Medicines Agency, Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. 24 October 2013.

²⁴ Food and Drug Administration, Guidance for Industry: complicated urinary tract infections and pyelonephritis-developing antimicrobial drugs for treatment. February 2012.

(94.9%) completed the study (513 [94.5%] and 515 [95.4%] in the ceftolozane/tazobactam and levofloxacin groups, respectively).

Less than 2% of randomised subjects (9 subjects [1.7%; 9/543] in the ceftolozane/tazobactam group and 6 [1.1%; 6/540] in the levofloxacin group) did not receive study treatment, and hence the MITT population was similar to the ITT population. The proportion of subjects included in the ME at TOC and mMITT populations were similar between treatment groups (ME at TOC: 340 subjects [62.6%; 340/543] and 353 subjects [65.4%; 353/540] in the ceftolozane/tazobactam and levofloxacin groups, respectively; mMITT: 398 subjects [73.3%; 398/543] and 402 subjects [74.4%; 402/540], respectively). Reasons for exclusion from the ME at TOC population were also generally comparable between the 2 treatment groups.

7.1.1.1.10. Major protocol violations/deviations

Frequency of protocol deviations was similar across treatment groups (63.5% [345/543] and 65.7% [355/540] in the ceftolozane/tazobactam and levofloxacin groups, respectively). The most frequently reported deviations in each treatment group were related to timing or collection of study assessments (42.0% [228/543] and 45.2% [244/540] in the ceftolozane/tazobactam and levofloxacin groups, respectively).

Study drugs were administered by the investigator or designee and all drug administration data were reported in the electronic case report form (eCRF) and the subjects' medical records. Treatment compliance was documented in the eCRF, including dates, start and stop times, dose, and quantity of study drug infused. Treatment compliance (defined as receiving $\geq 80\%$ and $\leq 120\%$ of the prescribed dose) was high in both treatment groups for ME at TOC population (100% in both treatment groups) and mMITT population (99.0% and 97.8% in the ceftolozane/tazobactam and levofloxacin groups, respectively).

7.1.1.1.11. Baseline data

Baseline demographic characteristics were comparable between treatment groups in the ME at TOC population. The majority of subjects in each treatment group were White (86.5% and 86.4% in the ceftolozane/tazobactam and levofloxacin groups, respectively) and female (71.8% and 75.1%, respectively). The mean (standard deviation [SD]) age was 48.5 (19.64) and 48.4 (20.23) years, respectively. Baseline mean body mass index (BMI) was similar between treatment groups (mean [SD] BMI of 25.32 [5.360] and 26.14 [5.683], respectively). Baseline demographic characteristics were also comparable between treatment groups in the mMITT population.

Baseline disease characteristics were also generally comparable between treatment groups in the ME at TOC and mMITT populations. In the ME at TOC population, the distribution of subjects by baseline cUTI diagnosis (cLUTI versus pyelonephritis) was similar between the 2 treatment arms (82.4% and 81.3% of subjects in the ceftolozane/tazobactam and levofloxacin groups, respectively, had pyelonephritis as baseline cUTI diagnosis). Baseline clinical signs and symptoms were generally similar between the 2 treatment groups. All subjects with pyelonephritis and all subjects with cLUTI had 2 or more symptoms. The most common uropathogen identified in each treatment group was *E. coli* (76.8% and 80.5% in the ceftolozane/tazobactam and levofloxacin groups, respectively). Overall, 7.2% of subjects had bacteraemia (7.1% and 7.4% in the ceftolozane/tazobactam and levofloxacin groups, respectively). The most common blood pathogen identified in each treatment group was *E. coli* (4.7% and 4.5%, respectively).

Comments: Overall, the baseline demographic and disease characteristics were comparable between treatment groups. The study population was generally representative of the target population of patients with cUTI requiring parenteral antibiotics.

7.1.1.2. Results for the primary and key secondary efficacy outcome

Primary and key secondary efficacy analyses showed that ceftolozane/tazobactam was non-inferior compared to levofloxacin in the treatment of adult subjects with cUTI (including pyelonephritis) in terms of microbiological success rate at the TOC visit in the ME at TOC population (primary efficacy analysis; microbiological success rate of 84.7% with ceftolozane/tazobactam vs. 75.4% with levofloxacin; treatment difference of 9.4% [99% CI:1.54, 17.12]) and in the mMITT population (key secondary efficacy analysis; microbiological success rate of 78.6% vs. 69.9%; treatment difference of 8.7% [99% CI: 0.77, 16.57]). The lower bound of the 2-sided 99% CI around the treatment differences (ceftolozane/tazobactam minus levofloxacin) was greater than -10% for both analyses.

7.1.1.3. Results for other efficacy outcomes

7.1.1.3.1. Supportive and sensitivity analyses on the primary and key secondary endpoints

The results of supportive and sensitivity analyses were generally consistent with the primary efficacy analyses, showing non-inferiority of ceftolozane/tazobactam compared to levofloxacin in terms of microbiological response rate at the TOC visit.

7.1.1.3.2. Subgroup analyses on the primary and key secondary endpoints

Subgroup analyses of the microbiological response rates at the TOC visit for the ME at TOC population and for the mMITT population yielded results that were generally consistent for the primary and key secondary outcomes, with ceftolozane/tazobactam comparing favourably with levofloxacin (ME at TOC population).

7.1.1.3.3. Other efficacy analyses

Analyses of the microbiological response rate at the EOT visit showed that ceftolozane/tazobactam had greater microbiological eradication rates compared to levofloxacin in both the ME at TOC and mMITT analysis populations. The results were also in favour of ceftolozane/tazobactam when analyses were broken down by baseline diagnosis.

With regards to microbiological response rate at the LFU visit, results showed that sustained microbiological eradication rate was lower in the ceftolozane/ tazobactam group (71.4%) compared to the levofloxacin group (81.4%), although the rate of relapses at the LFU visit was low for both study drugs (28.6 % and 15.9% in the ceftolozane/tazobactam and the levofloxacin groups, respectively).

Analyses of the clinical response rates at TOC visit showed that clinical cure rates at the TOC visit were high in both treatment groups, and higher in the ceftolozane/tazobactam group compared to the levofloxacin group in the ME at TOC population (95.9% vs. 93.2%) as well as in the mMITT population (92.0% vs. 88.6%). Microbiological response rates at the TOC visit were lower than clinical response rates at the same visit in both treatment groups (ceftolozane/tazobactam: microbiological success rate of 84.7% vs. clinical cure rate of 95.9% [ME at TOC population]; levofloxacin: 75.4% vs. 93.2% [ME at TOC population]). The sponsor had offered the opinion that this difference was expected and was indicative of asymptomatic bacteriuria detected at the TOC visit. Further analyses showed that there was a high concordance between microbiological success and clinical cure: the number of subjects that were a microbiological success and clinical failure at TOC visit was low, occurring in 17 subjects (2.5%; 17/693) in the ME at TOC population. These subjects with discordant clinical and microbiological outcomes were distributed equally between the 2 treatment arms (9 subjects in the ceftolozane/tazobactam treatment arm and 8 subjects in the levofloxacin treatment arm).

Analyses of the clinical response rates at EOT visit showed that clinical cure rates at the EOT visit were comparably high between ceftolozane/tazobactam and levofloxacin groups in the ME at TOC population (97.4% vs. 96.6%) as well as in the mMITT population (94.2% vs. 92.3%).

Analyses of the clinical response rates at LFU visit showed that sustained clinical response rates at the LFU visit were also comparably high between ceftolozane/tazobactam and levofloxacin groups in the CE at LFU population (96.4% vs. 95.4%).

Following 7 days of study therapy, the incidence of emergent infections (superinfections and/or new infections) was low in both treatment groups. The incidence of superinfections was 3.8% in the ceftolozane/tazobactam treatment arm and 5.7% in the levofloxacin treatment arm. The incidence of new infections was 8.8% in the ceftolozane/tazobactam treatment arm and 6.5% in the levofloxacin treatment arms.

Per-pathogen microbiologic eradication rates for common baseline uropathogens at the TOC visit for the ME at TOC population is summarised. Overall, ceftolozane/ tazobactam showed greater microbiologic eradication rates compared to levofloxacin for gram-negative aerobes (87.6% vs. 75.0%), and lower microbiologic eradication rates compared to levofloxacin for gram-positive aerobes (33.3% vs. 80.0%). The sponsor had offered the rationale that the enterococcal isolates (gram-positive aerobes) were known to be inherently resistant to cephalosporins.

Additional analyses showed that the by-subject microbiological response at the TOC visit was higher with ceftolozane/tazobactam compared to levofloxacin among subjects with ESBL-producing pathogens in the ME at TOC and mMITT populations based on a 99% CI.

Analyses showed that the incidence of emergence of resistance was low in the ceftolozane/ tazobactam treatment arm, where only 2 (0.6%) of the persisting pathogens developed resistance (one *E. coli* isolate and one *P. aeruginosa* isolate) among the 52 microbiological failures in the ceftolozane/tazobactam treatment arm with baseline and post-baseline isolates available for susceptibility testing. Levofloxacin-resistance on therapy developed in 14 of the levofloxacin-treated subjects in the ME at TOC population, out of 87 microbiological failures.

7.2. Evaluator's conclusions on efficacy for the treatment of complicated urinary tract infection, including pyelonephritis

Overall, the study design, study inclusion and exclusion criteria, and study endpoints of the pivotal study were appropriate. The study primary and secondary endpoints allowed evaluations of microbiological and clinical effects after 7 days of treatment at 7 days after the last dose of study drug (TOC visit), at within 24 hours after the last dose of study drug (EOT visit), and at 28 to 35 days after the last dose of study drug (LFU visit). Baseline demographic and disease characteristics were comparable between treatment groups and were consistent with the target patient population.

Efficacy results were generally supportive of the use of ceftolozane/tazobactam in the treatment of cUTI (including pyelonephritis) in terms of microbiological as well as clinical response. Primary and key secondary efficacy analyses showed that ceftolozane/tazobactam was non-inferior compared to levofloxacin in the treatment of adult subjects with cUTI (including pyelonephritis) in terms of microbiological success rate at the TOC visit in both the ME at TOC population (microbiological success rate of 84.7% with ceftolozane/tazobactam vs. 75.4% with levofloxacin; treatment difference of 9.4% [99% CI:1.54, 17.12]) and the mMITT population (microbiological success rate of 78.6% vs. 69.9%; treatment difference of 8.7% [99% CI: 0.77, 16.57]).

Analyses of the microbiological response rate at the EOT visit showed that ceftolozane/tazobactam had higher microbiological eradication rates compared to levofloxacin in both the ME at TOC (microbiological success rate of 95.6% with ceftolozane/tazobactam vs. 84.4% with levofloxacin; treatment difference of 11.2% [95% CI:6.79, 15.66]) and mMITT analysis populations (microbiological success rate of 94.2% with ceftolozane/tazobactam vs. 83.8% with levofloxacin; treatment difference of 10.4% [95% CI:6.12, 14.74]). However,

sustained microbiological eradication rate (microbiological response rate at the LFU visit) was lower in the ceftolozane/tazobactam group compared to the levofloxacin group ((71.4% vs. 81.4%; treatment difference of -12.7% [95% CI: -27.84, 4.20]), although the rate of relapses at the LFU visit was low for both study drugs (28.6% and 15.9% in the ceftolozane/tazobactam and the levofloxacin groups, respectively). It is noted that analyses of microbiological response rate at the LFU visit involved a small sample size. The sponsor had stated that as a urine culture was not required at the LFU visit unless a subject had signs and symptoms suggestive of recurrence of the urinary infection and as subjects were not required to return to the study centre for the LFU visit (which could be performed by phone), only 14% (100/693) of subjects in the ME at TOC population returned to the study centres for the LFU visit, had a urine specimen obtained and were microbiologically evaluable at the LFU visit.

With regards to clinical response rates, analyses showed that clinical cure rates were comparably high in both treatment groups at TOC visit (ME at TOC population: 95.9% with ceftolozane/tazobactam vs. 93.2% with levofloxacin; mMITT population: 92.0% vs. 88.6%) and at EOT visit (ME at TOC population: 97.4% vs. 96.6%; mMITT population: 94.2% vs. 92.3%). Sustained clinical response rates at the LFU visit were also comparably high between ceftolozane/tazobactam and levofloxacin groups in the CE at LFU population (96.4% vs. 95.4%).

The incidence of emergent infections (superinfections and/or new infections) following 7 days of study therapy was low in both treatment groups (incidence of superinfections: 3.8% with ceftolozane/tazobactam vs. 5.7% with levofloxacin; incidence of new infections: 8.8% vs. 6.5%).

7.3. For the indication of treatment of complicated intra-abdominal infections in combination with metronidazole

7.3.1. Pivotal efficacy studies

7.3.1.1. Study report CXA-cIAI-10-08-09

7.3.1.1.1. Study design, objectives, locations and dates

Studies CXA-cIAI-10-08 and CXA-cIAI-10-09 were multi-centre, randomised, double-blind, active-controlled study comparing the safety and efficacy of intravenous ceftolozane/tazobactam plus metronidazole with intravenous meropenem in complicated intra-abdominal infections (cIAI). The primary objective was to demonstrate the non-inferiority of ceftolozane/tazobactam plus metronidazole versus meropenem in adult subjects with cIAI based on the difference in clinical cure rates ([ceftolozane/tazobactam plus metronidazole] minus meropenem) at the Test-of-Cure (TOC) visit in the Clinically Evaluable (CE) population using a non-inferiority margin of -12.5%, at a 1-sided 0.005 significance level. The key secondary objective was to demonstrate the non-inferiority of ceftolozane/tazobactam plus metronidazole versus meropenem in adult subjects with cIAI based on the difference in clinical cure rates at the TOC visit in the Intent-to-Treat (ITT) population using a non-inferiority margin of -12.5%, at a 1-sided 0.005 significance level.

Studies CXA-cIAI-10-08 and CXA-cIAI-10-09 were multi-centre studies involving 196 sites across the 2 studies (102 study sites in study CXA-cIAI-10-08 and 94 study sites in study CXA-cIAI-10-09). Of these, 128 sites across 28 countries (67 sites versus 61 sites in studies CXA-cIAI-10-08 and CXA-cIAI-10-09, respectively) enrolled at least 1 subject. Overall, 83 enrolling sites (64.8% of enrolling sites) were in 16 European countries²⁵ and 54 enrolling sites (42.2% of enrolling sites) were in 12 European Union Member States²⁶. The study start dates (first subject enrolled) were 08 December 2011 and 11 April 2012 for studies CXA-cIAI-10-08 and CXA-cIAI-

²⁵ Belgium, Bulgaria, Croatia, Estonia, Georgia, Germany, Hungary, Latvia, Lithuania, Moldova, Poland, Romania, Russian Federation, Serbia, Slovakia, Spain, Ukraine.

²⁶ Belgium, Bulgaria, Croatia, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Spain.

10-09, respectively. The study completion dates (last subject completed) were 10 September 2013 and 15 October 2013, respectively.

Eligible subjects were randomised (stratified by investigational site and primary site of infection) in a 1:1 ratio to receive IV infusions of either ceftolozane/tazobactam (1.5g every 8 hours) and metronidazole (500mg every 8 hours) or meropenem (1g every 8 hours) and placebo (saline solution every 8 hours). Subject participation consisted of 3 phases: screening (baseline; Day -1 to Day 1 before first dose of study drug), treatment (Day 1 to Day 10), and post-treatment which comprises of End-of-therapy (EOT) visit (within 24 hours after the last dose of study drug), Test-of-cure (TOC) visit (26 to 30 days after the first dose of study drug), and Late follow-up (LFU) visit (38 to 45 days after the first dose of study drug). There were 3 daily doses consisting in total of 6 daily IV infusions (3 infusions of ceftolozane/tazobactam plus 3 infusions of metronidazole or 3 infusions of meropenem plus 3 dummy saline infusions) for subjects in each randomised treatment arm. Hospitalisation was mandatory during administration of at least the first 9 doses (approximately 3 days) of IV study therapy.

7.3.1.1.2. Inclusion and exclusion criteria

Subjects enrolled in the study were adult (≥ 18 years of age) males (practising reliable birth control methods) or females (not of child-bearing potential or practising reliable birth control methods) with cIAI (with evidence of intraperitoneal infection) requiring a surgical intervention within 24 hours (before or after) of the first dose of study drug, and had evidence of systemic infection. Subjects enrolled pre-operatively had to have radiographic evidence of bowel perforation or intra-abdominal abscess. Subjects who failed prior antibacterial treatment for the current IAI were enrolled but had to have a positive baseline culture from an intra-abdominal site and had to require surgical intervention.

Subjects were excluded if they had received any systemic antibiotic therapy for IAI for more than 24 hours prior to the first dose of study drug, unless there was a documented treatment failure with such therapy. Subjects with an IAI or post-operative infection caused by pathogen(s) resistant to meropenem prior to randomisation were also excluded

Comments: The inclusion and exclusion criteria were appropriate and consistent with the TGA-adopted EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections and the addendum to this guideline, as well as the FDA Guidance for Industry on complicated intra-abdominal infections: developing drugs for treatment.

7.3.1.1.3. Study treatments

Eligible subjects were randomised in a 1:1 ratio to receive IV infusions of either ceftolozane/tazobactam (1.5g every 8 hours) and metronidazole (500mg every 8 hours) or meropenem (1g every 8 hours) and matching placebo (saline solution every 8 hours). Subjects remained on study drugs for a minimum of 4 days (unless clinical failure occurred earlier or an adverse event [AE] necessitated early discontinuation) or up to 10 days. After 4 days, and at the discretion of the investigator, study drug administration was discontinued if the subject had signs and symptoms of clinical improvement (such as white blood cell [WBC] count $<12\,500/\mu\text{L}$; maximum oral temperature $<100.4^\circ\text{F}/38^\circ\text{C}$ for >24 hours without the influence of antipyretic agents; improvement of abdominal signs and symptoms manifested at study entry; return of bowel function and restoration of oral/enteral intake; no further antibiotic therapy was required). Subjects received up to 14 days of treatment with study drugs only if they did not meet study drug discontinuation criteria by Study Day 10 and had 1 or more of the following: multiple (≥ 2) abscesses; diffuse peritonitis from a source other than appendix; failure of prior therapy and a source other than appendix; hospital-acquired infection. Dose adjustments for renal insufficiency were performed by an unblinded pharmacist following notification from the

investigator of the subject's creatinine clearance (CL_{CR})²⁷. Subjects who developed severe renal failure ($CL_{CR} < 30$) were withdrawn from study drug administration because guidance for dose adjustment of ceftolozane/tazobactam in severe renal-impairment was not available at the time the studies were conducted.

Comments: The study dose selection is appropriate. The dose selection for ceftolozane/tazobactam has been previously discussed below. The choice of comparing ceftolozane/tazobactam with metronidazole against meropenem as active comparator is appropriate and consistent with clinical practice guidelines²⁸ where recommended antibiotic regimen for cIAI included combined use of a cephalosporin with metronidazole or a single agent of a carbapenem. The treatment duration of 4 to 10 days is also consistent with these clinical practice guidelines. Both metronidazole and meropenem are currently approved for use in Australia, and approved indications include the treatment of IAIs. The dose regimens used in the studies are the recommended dosing regimens in the respective approved Product Information.²⁹

7.3.1.1.4. Efficacy variables and outcomes

The primary efficacy endpoint was the clinical cure rate at the Test-of-Cure (TOC) visit in the clinically evaluable (CE) population. The key secondary efficacy endpoint was the clinical cure rate at the TOC visit in the Intent-to-Treat (ITT) population. Other secondary efficacy variables included the clinical cure rate at the TOC visit in the ME, MITT and Expanded ME populations; clinical cure rates at the EOT and LFU visits in the CE, ITT, ME, MITT and Expanded ME populations; per-subject microbiological success rates at the TOC visit in the ME, MITT and Expanded ME populations; per-pathogen microbiological response rates at the TOC visit in the ME, MITT and Expanded ME populations; proportion of subjects with superinfections or new infections in the MITT and ME populations.

Definitions for clinical response at the EOT and TOC visits are summarised. The investigator classified clinical outcomes at the EOT and TOC visits as clinical cure, clinical failure, or indeterminate. Failure was carried forward (i.e. subjects who were assessed as a failure prior to the TOC visit had "failure" recorded on the TOC outcome visit of the eCRF). Subjects who were clinically cured at the TOC visit were reassessed at the LFU visit for evidence of sustained clinical cure or relapse of symptoms. The sustained clinical cure rate was defined as the proportion of subjects in the relevant population with a response of sustained clinical cure at the LFU visit.

With regards to per-subject microbiological outcomes, an overall microbiological response for each subject was determined based on individual microbiological responses for each baseline pathogen at both the EOT and TOC visits. In order for the subject to have a favourable overall

²⁷ Dose adjustments based on renal function for ceftolozane/tazobactam: $CL_{CR} > 50$ mL/min and above- no dose adjustment required; $CL_{CR} 30-50$ mL/min- decrease dose to 750mg IV every 8 (± 2) hours (750mg ceftolozane/tazobactam = 500mg ceftolozane/250 mg tazobactam); $CL_{CR} < 30$ mL/min- discontinue study drug. No changes to the metronidazole dose were required for renal insufficiency. Dose adjustments based on renal function for meropenem: $CL_{CR} > 50$ mL/min- no dose adjustment required; $CL_{CR} 30-50$ mL/min- decrease meropenem dose to 1g IV every 12 (± 2) hours; $CL_{CR} < 30$ mL/min: discontinue study drug. As a dose adjustment of meropenem in moderate renal insufficiency required a change to 12-hourly dosing, additional two 1-hour dummy saline infusions 12 (± 2) hours following the first infusion of the day was administered to subjects in the ceftolozane/tazobactam plus metronidazole group with $CL_{CR} 30$ to 50 mL/min in order to maintain the study blind.

²⁸ Solomkin JS et al., Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. Vol 50 issue 2:133-64, 2010; Sartelli M, et al., 2013 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg. 8:3, 2013.

²⁹ Australia Product Information, Metronidazole. 30 October 2013; Australia Product Information, Meropenem. 12 May 2014.

microbiological response (i.e. microbiological success), each baseline pathogen had to have a favourable microbiological outcome. If the outcome for any pathogen was unfavourable, the subject was considered an overall microbiological failure. Microbiological response categories were eradication, presumed eradication, persistence, persistence acquiring resistance, presumed persistence, and indeterminate. Favourable microbiological responses (i.e. success) included “eradication” or “presumed eradication”. Unfavourable responses included “persistence,” “persistence acquiring resistance,” and “presumed persistence”. With regards to per-pathogen microbiological outcomes, a microbiological response for each pathogen isolated at baseline was determined at both the EOT and TOC visits.

Comments: The primary and secondary endpoints are appropriate and consistent with the TGA-adopted EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections and the addendum to this guideline, as well as the FDA Guidance for Industry on complicated intra-abdominal infections: developing drugs for treatment. Overall, the study primary and secondary endpoints allowed evaluations of clinical and microbiological effects after 4 to 10 days of treatment at 26 to 30 days after the first dose of study drug (TOC visit), at within 24 hours after the last dose of study drug (EOT visit), and at 38 to 45 days after the first dose of study drug (LFU visit).

7.3.1.1.5. Randomisation and blinding methods

Eligible subjects were randomised in a 1:1 ratio to receive IV infusions of either ceftolozane/tazobactam (1.5g) plus metronidazole (500mg) or meropenem (1g) plus matching saline placebo. After informed consent was obtained and study eligibility was established, the study site’s pharmacist obtained, via the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS), the subject number and the study drug assignment from a centralised computer-generated randomisation schedule. Block randomisation, stratified by study site and primary site of infection, was used to assign subjects to treatment groups. The studies were double-blind. Blinding was achieved using placebo dummy saline infusions. The saline infusion following meropenem administration was given for the same duration as the metronidazole infusion that followed the ceftolozane/tazobactam infusion.

7.3.1.1.6. Analysis populations

There were 8 analysis population sets in the study. The Intent-to-Treat (ITT) population was defined as 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. The Microbiological Intent-to-Treat (MITT) population consisted of all randomised subjects (regardless of whether or not the subjects went on to receive study drug) who had IAI as evidenced by identification of at least 1 baseline intra-abdominal pathogen identified, regardless of susceptibility to study drug. Subjects in the MITT population were categorised based on the treatment that subjects were randomised to, irrespective of what they actually received. The Clinically Evaluable (CE) population was a subset of the ITT population of subjects who received an adequate duration of study drug therapy, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a TOC visit within the specified visit window. The Microbiologically Evaluable (ME) population was the subset of the CE subjects who had at least 1 baseline infecting intra-abdominal pathogen identified that was susceptible to study drug. The Expanded Microbiologically Evaluable (expanded ME) population consisted of all subjects in the MITT population who met all CE population criteria. The Clinically Evaluable at Late Follow-up (CE at LFU) population was a subset of the CE population and included all subjects who were clinical cures at the TOC visit and had an LFU assessment. The Microbiologically Evaluable at Late Follow-up (ME at LFU) population was a subset of the ME population and included all subjects who were clinical cures at the TOC visit and had an LFU assessment. The Safety population included all subjects who received any amount of study drug. Subjects in the Safety population

were categorised based on the actual treatment that the subjects received, irrespective of the treatment to which they were randomised.

The primary and key secondary efficacy analyses were based on the CE and ITT populations, respectively. The safety analyses were based on the Safety population.

Comments: The definitions of the analysis populations and the efficacy analyses on the CE and ITT populations are in keeping with the TGA-adopted EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections and the addendum to this guideline. These guideline recommendations were generally similar to those in the FDA Guidance for Industry on complicated intra-abdominal infections: developing drugs for treatment except that the FDA required the primary analysis population to be the MITT population (i.e. all randomised subjects who had at least 1 baseline IAI pathogen isolated), while the EMA guidances indicated that “it is not required that the primary analysis should be confined to the subset of patients with at least one acceptable baseline pathogen”. According to the sponsor, based on this consideration and in order to include the maximum number of subjects in the primary analysis population, the primary analysis for the EMA (and TGA) submissions was conducted in the per-protocol CE population with the key secondary analysis conducted in the ITT population. As previously described, the sponsor had confirmed that while the submission dossier for Australia is identical to the dossier submitted to the EMA, the clinical trial data in the US submission was presented differently to the EMA and Australian submissions, due to pre-submission discussions with the EMA, FDA and TGA on recommended/acceptable primary and secondary endpoints and statistical analysis.

7.3.1.1.7. Sample size

It was estimated that a combined sample size of 988 subjects (494 subjects per arm) would be needed to provide approximately 370 clinically evaluable subjects per treatment arm (based on assumption that 75% of randomised subjects would meet the criteria to be included in the CE population). This would provide the combined study (i.e. pooled studies CXA-cIAI-10-08 and CXA-cIAI-10-09) with an overall power of approximately 99% to demonstrate non-inferiority of ceftolozane/tazobactam plus metronidazole to meropenem at a 12.5% non-inferiority margin at a 1-sided alpha level of 0.005 in terms of the primary efficacy hypothesis. This sample size estimation was based on an assumed clinical cure rate of 86.6% for both groups.

7.3.1.1.8. Statistical methods

The primary and key secondary efficacy hypotheses were to establish non-inferiority of ceftolozane/tazobactam plus metronidazole versus meropenem in the CE and ITT populations, respectively, based on the proportion of subjects who achieved clinical cure at the TOC visit. The hypotheses were tested at the 1-sided 0.005 significance level, through a 2-sided 99% confidence interval (CI) approach. The 2-sided 99% CI on the difference of proportions for ceftolozane/tazobactam plus metronidazole minus comparator (meropenem) was constructed using stratified Newcombe CI with Minimum Risk weights. Non-inferiority was concluded if the lower bound of the 2-sided 99% CI was greater than -12.5% (non-inferiority margin), in the CE population and the ITT population for the primary and key secondary efficacy analysis, respectively. The randomisation in each of the individual protocols was stratified by investigational sites and primary site of infection, but due to the large number of investigational sites and relatively small sample size expected at each site, the primary and key secondary analyses were adjusted with the stratification factor of region³⁰ and primary site of infection.

³⁰ Region was categorised as: Eastern Europe (Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Republic of Moldova, Romania, Russia, Serbia, Slovakia, Ukraine); Western Europe (Spain, Belgium, Germany); North America (Mexico, USA); South America (Argentina, Brazil, Chile, Colombia, Peru); and Rest of World (Australia, Israel, South Africa, South Korea).

As a supportive analysis, unstratified analyses with a 2-sided 99% Wilson Score CI for individual proportions and proportion differences (treatment – control) were also performed for the primary and key secondary efficacy endpoints. In addition, several other sensitivity analyses were performed for the primary and key secondary efficacy variables to assess the robustness of the results. Subgroup analyses (exploratory) were also performed on the primary and key secondary efficacy endpoints.³¹

For clinical responses, missing or indeterminate responses were primarily handled with a data as observed (DAO) approach for the CE, ME, and Expanded ME populations (i.e. missing or indeterminate responses were excluded), and a treatment failure approach (TFA) for the ITT and MITT populations, which was defined in the Statistical Analysis Plan as: for the analysis of clinical response at the TOC visit in the ITT and MITT populations, subjects with a missing clinical response, including indeterminate, were categorised as treatment failures; a missing clinical outcome at the TOC visit was considered an indeterminate outcome unless the clinical outcome at the EOT visit was failure (a clinical outcome of failure at the EOT visit was carried forward to the TOC visit). For microbiological responses, missing data were handled with a DAO approach for the ME and Expanded ME populations and a treatment failure approach for the MITT population.

Comments: The non-inferiority margin of -12.5% is appropriate and consistent with the addendum to the EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections³² which stated that “a non-inferiority margin of -12.5% is suggested” for cIAI. In addition, the sponsor had provided in the Statistical Analysis Plan the justification for the non-inferiority margin (NI) of -12.5%. The fixed margin approach (using 95% confidence interval) was used to justify the NI margin. A meta-analysis using non-iterative weighted DerSimonian and Laird random effect model was used to estimate the active control effect versus placebo infusion in the cIAI population. The analysis showed that the conservative active control effect (derived from prophylactic studies) was 31.2%. After discounting the estimated active control effect by 50% (M1=15.6%), taking a conservative approach, the clinically relevant non-inferiority margin (M2) of 12.5% was estimated to still be able to ensure the preservation of approximately 20.0% of the active control effect. The rationale for the non-inferiority margin is generally consistent with the relevant FDA, EMA and ICH guidelines on non-inferiority statistical analyses.³³

7.3.1.1.9. Participation flow

A total of 993 subjects were enrolled and randomised: 487 to the ceftolozane/tazobactam + metronidazole group, and 506 to the meropenem group. Twenty-three of these randomised subjects (11 in the ceftolozane/tazobactam + metronidazole group and 12 in the meropenem group) from 2 study sites were excluded from the ITT population for the evaluation of efficacy due to finding of GCP non-compliance with potential risk for integrity of data collected at these sites. Thus the ITT population included 970 subjects with 476 subjects in the ceftolozane/tazobactam + metronidazole treatment arm and 494 subjects in the meropenem arm. A total of 906 subjects (93.4%) in the ITT population completed the study (442 [92.9%] and 464 [93.9%] in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively).

³¹ Subgroup analyses included age category, APACHE (Acute Physiology and Chronic Health Evaluation) II score, renal function at baseline, infectious process (local or diffuse peritonitis, single or multiple abscesses).

³² European Medicines Agency, Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. 24 October 2013.

³³ European Medicines Agency, Guideline on the Choice of the Non-Inferiority Margin. 27 July 2005; Food and Drug Administration, Guidance for Industry: Non-Inferiority Clinical Trials. March 2010; ICH Efficacy Guidelines. E9: Statistical Principles for Clinical Trials. September 1998.

The percentage of subjects in the analysis populations was generally similar between the 2 treatment arms. The reasons for exclusion from the MITT, CE, and expanded ME populations were generally similar in the 2 treatment arms.

Comments: The sponsor had not provided in the CSR any details regarding the issues of GCP non-compliance at the 2 study sites, justification for the exclusion of the 23 randomised subjects enrolled at these 2 sites from the ITT population or when the decision to exclude these subjects were made (e.g. before or after unblinding). This will be raised as clinical question for the sponsor.

7.3.1.1.10. Major protocol violations/ deviations

Frequency of protocol deviations was similar between treatment groups (59.7% [284/476] and 59.1% [292/494] in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively). The most frequently reported deviations in each treatment group were related to timing or collection of study assessments (36.6% [174/476] and 37.2% [184/494] in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively).

Study drugs were administered by the investigator or designee and all drug administration data were reported in the eCRF and the subjects' medical records. Treatment compliance was documented in the eCRF including dates, start and stop times, dose, and quantity of study drug infused. Treatment compliance (defined as receipt $\geq 80\%$ and $\leq 120\%$ of the prescribed dose) was high in both treatment groups for the ITT (95.8% in both treatment groups), MITT (95.9% in both treatment groups), CE (100% in both treatment groups), ME (100% in both treatment groups) and safety (96.7% in both treatment groups) populations.

7.3.1.1.11. Baseline data

Baseline demographic characteristics were comparable between treatment groups in the ITT population. The majority of subjects in each treatment group were White (94.1% and 92.9% in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively) and male (55.9% and 60.7%, respectively). The mean (SD) age was 50.7 (17.93) and 50.7 (16.83) years, respectively. Baseline mean BMI was similar between treatment groups (mean [SD] BMI of 26.82 [5.451] and 27.03 [5.087], respectively). Baseline demographic characteristics were also comparable between treatment groups in the CE population.

Baseline disease characteristics were also generally comparable between treatment groups in the ITT and CE populations (ITT population). In the ITT population, the most common diagnosis was appendiceal perforation or peri-appendiceal abscess (42.6% and 43.9% of subjects in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively). Peritonitis was present at baseline in 83.6% and 80.2% of subjects, respectively. Baseline clinical signs and symptoms were generally similar between the 2 treatment arms. The most common intra-abdominal pathogens identified in each treatment group was *E. coli* (65.6% and 64.7% in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively).

Comments: Overall, the baseline demographic and disease characteristics were comparable between treatment groups. The study population was generally representative of the target population of patients with cIAI requiring parenteral antibiotics.

7.3.1.2. Results for the primary efficacy outcome

Primary and key secondary efficacy analyses showed that ceftolozane/tazobactam + metronidazole was non-inferior to meropenem in the treatment of adult subjects with cIAI in terms of clinical cure rate at the TOC visit in the CE population (primary efficacy analysis; clinical cure rate of 94.1% with ceftolozane/tazobactam + metronidazole vs. 94.0% with meropenem; treatment difference of 0.0% [99% CI:-4.16, 4.30]) and in the ITT population (key secondary efficacy analysis; clinical cure rate of 83.8% vs. 85.8%; treatment difference of -2.2% [99% CI:-7.95, 3.44]). The lower bound of the 2-sided 99% CI around the treatment differences

([ceftolozane/tazobactam + metronidazole] minus meropenem) was greater than -12.5% for both analyses.

7.3.1.3. Results for other efficacy outcomes

7.3.1.3.1. Supportive and sensitivity analyses on the primary and key secondary endpoints

The results of supportive and sensitivity analyses were generally consistent with the primary efficacy analyses, showing non-inferiority of ceftolozane/tazobactam + metronidazole compared to meropenem in terms of clinical cure rate at the TOC visit.

7.3.1.3.2. Subgroup analyses on the primary and key secondary endpoints

Subgroup analyses of the clinical cure rate at the TOC visit for the CE and ITT populations yielded results that were consistent with the primary and key secondary outcomes, with generally comparable clinical cure rates between ceftolozane/tazobactam + metronidazole versus meropenem in the subgroups evaluated.

7.3.1.3.3. Other efficacy analyses

Analyses of the clinical cure rate at the TOC visit in the ME, MITT and Expanded ME populations showed generally comparable clinical cure rates between the ceftolozane/tazobactam + metronidazole group and the meropenem group (ME population: 94.2% vs. 94.7%; MITT population: 83.0% vs. 87.3%; Expanded ME population: 93.8% vs. 93.6%).

Analyses of the clinical cure rate at the EOT visit in the CE, ITT, ME, MITT and Expanded ME populations also showed generally comparable clinical cure rates between the ceftolozane/tazobactam + metronidazole group and the meropenem group (treatment difference [ceftolozane/tazobactam+metronidazole] minus meropenem of -3.1% to -0.1%). Sustained clinical cure (clinical cure at TOC with no signs or symptoms recurring or worsening since TOC at the LFU visit) rates in the CE, ITT, ME, MITT and Expanded ME populations were also comparable between the ceftolozane/tazobactam + metronidazole group and the meropenem group (treatment difference of -4.1% to 0.7%).

Analyses of the per-subject microbiological success rates at the TOC visit in the ME, MITT and Expanded ME populations showed that microbiological success rates at the TOC visit were comparable between the ceftolozane/tazobactam + metronidazole group and the meropenem group (treatment difference of -3.4% to 0.9%).

Per-pathogen microbiological eradication rates at the TOC visit in the ME, MITT and Expanded ME populations were also comparable between the ceftolozane/tazobactam + metronidazole group and the meropenem group (ME population), as were the per-pathogen clinical response rates at the TOC visit in the ME population.

The incidence of emergent infections (superinfections and/or new infections) was low in both treatment groups. The incidence of superinfections was 2.6% in the ceftolozane/tazobactam + metronidazole treatment arm and 3.1% in the meropenem treatment arm. The incidence of new infections was 3.1% and 2.2%, respectively. There was no documented emergence of decreased susceptibility or resistance in either treatment arm.

7.4. Evaluator's conclusions on efficacy for the treatment of complicated intra-abdominal infections in combination with metronidazole

Overall, the study design, study inclusion and exclusion criteria, and study endpoints of the pivotal study were appropriate. The study primary and secondary endpoints allowed evaluations of clinical and microbiological effects after 4 to 10 days of treatment, at 26 to 30 days after the first dose of study drug (TOC visit), at within 24 hours after the last dose of study drug (EOT visit) and at 38 to 45 days after the first dose of study drug (LFU visit). Baseline

demographic and disease characteristics were comparable between treatment groups and were consistent with the target patient population.

Efficacy results were generally supportive of the use of ceftolozane/tazobactam in the treatment of cIAI in terms of clinical as well as microbiological response. Primary and key secondary efficacy analyses showed that ceftolozane/tazobactam + metronidazole was non-inferior to meropenem in the treatment of adult subjects with cIAI in terms of clinical cure rate at the TOC visit in the CE population (clinical cure rate of 94.1% with ceftolozane/tazobactam + metronidazole vs. 94.0% with meropenem; treatment difference of 0.0% [99% CI:-4.16, 4.30]) and in the ITT population (clinical cure rate of 83.8% vs. 85.8%; treatment difference of -2.2% [99% CI:-7.95, 3.44]). Analyses of the clinical cure rate at the TOC visit in other analysis populations (ME, MITT and Expanded ME populations) also showed generally comparable clinical cure rates between the ceftolozane/tazobactam + metronidazole group and the meropenem group (ME population: 94.2% vs. 94.7%; MITT population: 83.0% vs. 87.3%; Expanded ME population: 93.8% vs. 93.6%), as did analyses of the clinical cure rate at the EOT visit in the various analysis populations (CE, ITT, ME, MITT and Expanded ME populations): treatment difference ([ceftolozane/tazobactam + metronidazole] minus meropenem) of -3.1% to -0.1%. Sustained clinical cure rates (at the LFU visit) in the CE, ITT, ME, MITT and Expanded ME populations were also comparable between the ceftolozane/tazobactam + metronidazole group and the meropenem group (treatment difference of -4.1% to 0.7%).

Per-subject microbiological success rates at the TOC visit were comparable between the ceftolozane/tazobactam + metronidazole group and the meropenem group in the ME, MITT and Expanded ME populations (treatment difference of -3.4% to 0.9%). In addition, the incidence of emergent infections (superinfections and/or new infections) was low in both treatment groups (incidence of superinfections: 2.6% with ceftolozane/tazobactam + metronidazole vs. 3.1% with meropenem; incidence of new infections: 3.1% and 2.2%, respectively).

8. Clinical safety

8.1. Studies providing safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies (study reports CXA-cUTI-10-04-05 and CXA-cIAI-10-08-09)

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by the investigator obtaining and recording all AEs at each scheduled visit. All AEs were classified by preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, version 14.1).
- Laboratory tests performed included serum haematology, coagulation tests (prothrombin time, direct coomb's test), clinical chemistry,³⁴ urinalysis and urine microscopy.

8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

³⁴ Including sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, albumin, total protein, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase [ALP], gamma-glutamyl transferase (GGT)calcium, phosphorus, uric acid, and non-fasting serum glucose.

8.3. Patient exposure

In CXA-cUTI-10-04-05, the mean (SD) length of exposure was 5.78 (1.81) days and 5.81 (1.72) days in the ceftolozane/tazobactam and levofloxacin groups, respectively. Overall, 77.1% of subjects in the ceftolozane/tazobactam group and 76.3% of subjects in the levofloxacin group were exposed to study treatment for at least 7 days.

In CXA-cIAI-10-08-09, the mean (SD) length of exposure was 7.7 (2.43) days and 7.6 (2.48) days in the ceftolozane/tazobactam + metronidazole and the meropenem groups, respectively. Overall, 83.8% of subjects in the ceftolozane/tazobactam + metronidazole group and 87.3% of subjects in the meropenem group were exposed to study treatment for 4 to 10 days.

Comments: Overall, the study drug exposure is adequate to assess the safety profile of ceftolozane/tazobactam.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

In CXA-cUTI-10-04-05, the percentages of subjects with any treatment emergent adverse events (TEAEs) were comparable between treatment groups (34.7% and 34.4% in the ceftolozane/tazobactam and levofloxacin groups, respectively). The most commonly reported AE by preferred term in the ceftolozane/tazobactam group were headache (5.8% with ceftolozane/tazobactam vs. 4.9% in the levofloxacin group) and constipation (3.9% vs. 3.2%). Most TEAEs were mild or moderate in intensity. The incidence of TEAEs of severe intensity was low and comparable across treatment groups (3.2% [17/533] of subjects in the ceftolozane/tazobactam group vs. 1.9% [10/535] of subjects in the levofloxacin group).

In CXA-cIAI-10-08-09, the percentages of subjects with any TEAEs were comparable between treatment groups (44.0% and 42.7% in the ceftolozane/tazobactam + metronidazole and the meropenem groups, respectively). For TEAEs that occurred in $\geq 1\%$ of subjects, the most commonly reported AE by preferred term in the ceftolozane/tazobactam + metronidazole group were nausea (7.9% vs. 5.8% in the meropenem group) and diarrhoea (6.2% vs. 5.0%). Most TEAEs were mild or moderate in intensity. TEAEs of severe intensity were reported in 7.5% [36/482] of subjects in the ceftolozane/tazobactam + metronidazole group and 5.6% [28/497] of subjects in the meropenem group).

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

In CXA-cUTI-10-04-05, the percentages of subjects with any treatment-related TEAEs were comparable between treatment groups (10.3% and 12.0% in the ceftolozane/tazobactam and levofloxacin groups, respectively). For treatment-related AEs that occurred in $>1\%$ of subjects in any treatment group, the most commonly reported treatment-related AE by preferred term in the ceftolozane/tazobactam group was headache (1.9% with ceftolozane/tazobactam vs. 0.9% in the levofloxacin group).

In CXA-cIAI-10-08-09, the percentages of subjects with any treatment-related TEAEs were comparable between treatment groups (8.1% and 8.9% in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively). For treatment-related AEs that occurred in $\geq 1\%$ of subjects, the most commonly reported treatment-related AE by preferred term in the ceftolozane/tazobactam + metronidazole group was diarrhoea (2.5% with ceftolozane/tazobactam + metronidazole vs. 2.4% in the meropenem group).

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

In CXA-cUTI-10-04-05, one death was reported in the ceftolozane/tazobactam group (vs. no deaths in the levofloxacin group). The subject in the ceftolozane/tazobactam group who died during the study was [information redacted] female from Poland who was diagnosed with a bladder neoplasm on Study Day 4 of study treatment. A tumour biopsy revealed Grade 3/4 uroepithelial carcinoma and palliative care was planned. The subject died from the bladder cancer 38 days after the end of study therapy. The death was assessed as unrelated to study treatment by both the investigator and the sponsor.

In CXA-cUTI-10-04-05, the percentage of subjects with any serious adverse events (SAEs) was comparable between treatment groups (2.8% [15/533] and 3.4% [18/535] in the ceftolozane/tazobactam and levofloxacin groups, respectively). The most commonly reported SAE by preferred term in the ceftolozane/tazobactam group was urinary tract infection (0.6% with ceftolozane/tazobactam vs. 0.4% in the levofloxacin group). Overall, only 2 SAEs (both in the ceftolozane/tazobactam treatment arm) were considered related to study treatment. The 2 drug-related SAEs were both cases of *C. difficile* infections (preferred terms of *Clostridium difficile* colitis and Pseudomembranous colitis, respectively).

In CXA-cIAI-10-08-09, 19 deaths were reported (11 [2.3%] and 8 [1.6%] in the ceftolozane/tazobactam + metronidazole and meropenem treatment arms, respectively). All TEAEs leading to death were judged to be unrelated to study treatment.

In CXA-cIAI-10-08-09, the percentage of subjects with any SAEs was comparable between treatment groups (8.1% [39/482] and 7.2% [36/497] in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively). The most commonly reported SAE by preferred term in the ceftolozane/tazobactam + metronidazole group was septic shock (0.6% with ceftolozane/tazobactam + metronidazole vs. 0.4% in the meropenem group) and multi-organ failure (0.6% vs. 0%). Overall, only 2 SAEs (one in each treatment arm) were considered related to study treatment. The 2 drug-related SAEs were both cases of *C. difficile* infections (preferred terms of *Clostridium difficile* colitis in both cases).

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

In CXA-cUTI-10-04-05, the percentage of subjects with any AEs leading to discontinuation of study drug was comparable between treatment groups (1.3% and 1.7% in the ceftolozane/tazobactam and levofloxacin groups, respectively). No AEs leading to discontinuation of study drug (preferred term) was reported by > 1 subject each. The percentage of subjects with any treatment-related AEs leading to discontinuation of study drug was low in both treatment groups (0.6% [3/533] and 1.1% [6/535] in the ceftolozane/tazobactam and levofloxacin groups, respectively).

In CXA-cIAI-10-08-09, the percentage of subjects with any AEs leading to discontinuation of study drug was comparable between treatment groups (2.7% and 2.2% in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively). No AEs leading to discontinuation of study drug (preferred term) was reported by > 1 subject each in the ceftolozane/tazobactam + metronidazole group, except for the TEAE of renal impairment (reported by 2 subjects [0.4%] vs. 0% in the meropenem group). The percentage of subjects with any treatment-related AEs leading to discontinuation of study drug was low in both treatment groups (0.6% [3/482] and 0.8% [4/497] in the ceftolozane/tazobactam + metronidazole and meropenem groups, respectively).

8.5. Laboratory tests

In CXA-cUTI-10-04-05 and CXA-cIAI-10-08-09, laboratory test results did not raise any safety concerns.

8.5.1. Clinical chemistry

8.5.1.1. Pivotal studies

In CXA-cUTI-10-04-05, clinical chemistry results did not raise any safety concerns. The incidence of significant shifts (≥ 2 Grades from baseline) in clinical chemistry parameters was low and generally comparable in both treatment arms. Analyses of median values and median changes from baseline to EOT and TOC visits for clinical chemistry parameters did not show any significant persistent trends in either treatment group. Incidences of significant transaminase and bilirubin elevations ($>3x$, $>5x$ or $>10x$ upper limit of normal [ULN] and $>1.5x$ ULN or $>2x$ ULN, respectively) were low in both treatment arms throughout the study period, and by the LFU visit all subjects in the ceftolozane/tazobactam treatment arm were below the designated ULN thresholds.

In CXA-cIAI-10-08-09, clinical chemistry results did not raise any safety concerns. The incidence of significant shifts (≥ 2 Grades from baseline) in clinical chemistry parameters was low and generally comparable in both treatment arms. Analyses of the mean baseline values and change from baseline to EOT for clinical chemistry parameters showed that changes from baseline to EOT were generally small and not clinically significant. Incidence of significant transaminase and bilirubin elevations ($>3x$ or $>5x$ or $>10x$ ULN and $>1.5x$ ULN or $>2x$ ULN, respectively) were low in both treatment arms throughout the study period.

8.5.2. Haematology

8.5.2.1. Pivotal studies

In CXA-cUTI-10-04-05 and CXA-cIAI-10-08-09, haematology, results did not raise any safety concerns. The incidence of significant shifts (≥ 2 Grades from baseline) in haematology laboratory parameters was generally low and comparable in both treatment arms.

8.5.3. Coagulation tests

8.5.3.1. Pivotal studies

In CXA-cUTI-10-04-05, analyses of coagulation test results did not raise any safety concerns. Analyses of median values and median changes from baseline to EOT and TOC visits for prothrombin time did not show any increasing trend in either treatment group. In CXA-cIAI-10-08-09, analyses of coagulation test results also did not raise any safety concerns. Analyses of the mean baseline values and change from baseline to EOT for prothrombin time did not show any increase in prothrombin time in either treatment group.

Analyses of Direct Coombs' tests showed that seroconversion from a negative to positive Coombs test from baseline to the EOT visit occurred in 1 subject in ceftolozane/tazobactam group in CXA-cUTI-10-04-05 (versus 0 subject in the levofloxacin group) and 1 subject in the ceftolozane/tazobactam + metronidazole group in CXA-cIAI-10-08-09 (versus 0 subject in the meropenem group). No other laboratory abnormalities or study findings were indicative of haemolytic anaemia in either of these subjects.

8.5.4. Urinalysis

8.5.4.1. Pivotal studies

In CXA-cUTI-10-04-05 and CXA-cIAI-10-08-09, analyses of urinalysis results did not raise any safety concerns.

8.5.5. Vital signs

8.5.5.1. Pivotal studies

In CXA-cUTI-10-04-05, analyses of vital signs did not raise any safety concerns. The mean changes in systolic and diastolic blood pressure (BP), heart rate, and temperature from baseline to EOT were small and similar between ceftolozane/tazobactam and levofloxacin. The proportion of subjects with potentially clinically significant changes in vital signs at EOT was comparably low in both treatment groups.

In CXA-cIAI-10-08-09, analyses of vital signs also did not raise any safety concerns. The mean changes in systolic and diastolic BP, heart rate, and temperature from baseline to EOT were small and similar between ceftolozane/tazobactam + metronidazole and meropenem. The proportion of subjects with potentially clinically significant changes in vital signs at EOT was comparably low in both treatment groups.

8.6. Post marketing experience

Not applicable.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

Transaminase elevations are associated with β -lactam antibiotics. Safety results showed that in CXA-cUTI-10-04-05 and CXA-cIAI-10-08-09 the incidence of raised ALT and AST as adverse events was low. In CXA-cUTI-10-04-05, the incidence of raised ALT as all-causality AEs was 1.7% with ceftolozane/tazobactam vs. 0.9% with levofloxacin, while that for raised AST was also 1.7% vs. 0.9%. The incidence of raised ALT as treatment-related AEs was 1.1% with ceftolozane/tazobactam vs. 0.7% with levofloxacin, while that for raised AST was 1.3% vs. 0.7%. In CXA-cIAI-10-08-09, the incidence of raised ALT as all-causality AEs was 1.5% with ceftolozane/tazobactam + metronidazole vs. 1.0% with meropenem, while that for raised AST was also 1.0% vs. 0.6%. The incidence of raised ALT as treatment-related AEs was 0.6% with ceftolozane/tazobactam + metronidazole vs. 0.6% with meropenem, while that for raised AST was also 0.6% vs. 0.6%. None of these transaminase elevations were SAEs or led to study drug discontinuation except for 1 subject (in ceftolozane/tazobactam + metronidazole group in CXA-cIAI-10-08-09) where an SAE was reported for the preferred term of "hepatic enzyme increased". In both CXA-cUTI-10-04-05 and CXA-cIAI-10-08-09, incidences of significant transaminase elevations ($>3x$, $>5x$ or $>10x$ ULN) were low in both treatment arms throughout the study period.

8.8. Other safety issues

8.8.1. Safety in special populations

Analyses of TEAEs by age subgroup showed that the incidence of treatment-related TEAEs in the ceftolozane/tazobactam (or ceftolozane/tazobactam + metronidazole) group was not higher in the ≥ 65 years age subgroup compared to the < 65 years age subgroup in CXA-cUTI-10-04-05 (8.2% in the ≥ 65 years age group vs. 11.0% in the < 65 years age group) and CXA-cIAI-10-08-09 (4.3% vs. 9.3%). The incidence of treatment-related SAEs in the ceftolozane/tazobactam (or ceftolozane/tazobactam + metronidazole) group was low and comparable between the ≥ 65 years and < 65 years age subgroups in CXA-cUTI-10-04-05 (0.7% [1 subject] in the ≥ 65 years age group vs. 0.3% [1 subject] in the < 65 years age group) and CXA-cIAI-10-08-09 (0.9% [1 subject] vs. 0%).

8.8.2. Antibacterial resistance

The sponsor has submitted antibacterial resistance risk data in Module 1. Overall, in-vitro, in-vivo, and clinical studies data indicated that ceftolozane/tazobactam had a low potential for development of antibacterial resistance. Bacterial resistance mechanisms that could compromise ceftolozane/tazobactam included drug inactivation by serine carbapenemases, such as *klebsiella pneumoniae* carbapenemase (KPC), and metallo-beta lactamases. Ceftolozane/tazobactam was found to be active against bacterial strains with common resistance mechanisms found in Gram-negative bacteria, including broad spectrum beta-lactamases (TEM-1, TEM-2, SHV-1), extended spectrum beta-lactamases (CTX-M-14, CTX-M-15, TEM-3, SHV-2), chromosomal pseudomonal AmpC, oxacillinases (OXA-2, OXA -5), loss of outer membrane porin (OprD) and upregulation of efflux pumps (MexXY, MexAB).

Single and multiple in-vitro passage studies, as well as 10-day hollow-fibre models, indicated that ceftolozane/tazobactam had a low potential for development of resistance in *P. aeruginosa* and ESBL-positive *E. coli*. In particular, ceftolozane was found to be stable to *P. aeruginosa* AmpC hydrolysis³⁵ because of its low affinity for the *P. aeruginosa* AmpC enzyme. In addition, ceftolozane was not a substrate for active efflux and was not affected by the loss of outer membrane protein D (OprD) in *P. aeruginosa*, thus allowing it to remain active against many bacterial strains resistant to carbapenems or other cephalosporins.

Assessments of emergence of resistance during clinical therapy showed low incidence of emergent resistance. In the cUTI studies (study report CXA-cUTI-10-04-05), both ceftolozane/tazobactam and levofloxacin had a low incidence of emergence of decreased susceptibility, with only 4 (1.0%) instances in the ceftolozane/tazobactam arm compared to 14 (3.5%) in the levofloxacin arm. There was also a low incidence of emergence of resistance, with only 2 (0.5%) instances in the ceftolozane/tazobactam arm compared to 16 (4.0%) in the levofloxacin arm. In the cIAI studies (study report CXA-cIAI-10-08-09), there was no emergence of decreased susceptibility or resistance in either treatment arm.

8.9. Evaluator's conclusions on safety

Overall, safety results did not raise any major safety concerns. For the indication of treatment of cUTI, safety results showed that the percentages of subjects with any AEs (34.7% with ceftolozane/tazobactam vs. and 34.4% with levofloxacin), treatment-related AEs (10.3% vs. 12.0%), SAEs (2.8% vs. 3.4%), and AEs leading to discontinuation of study drug (1.3% vs. 1.7%) were comparable between ceftolozane/tazobactam and levofloxacin. One death was reported in the ceftolozane/tazobactam group (vs. no deaths in the levofloxacin group), but the cause of death was considered unrelated to study treatment.

For the indication of treatment of cIAI in combination with metronidazole, safety results showed that the percentages of subjects with any AEs (44.0% with ceftolozane/tazobactam + metronidazole vs. and 42.7% with meropenem), treatment-related AEs (8.1% vs. 8.9%), SAEs (8.1% vs. 7.2%), and AEs leading to discontinuation of study drug (2.7% vs. 2.2%) were comparable between ceftolozane/tazobactam + metronidazole and meropenem. Eleven deaths (2.3%) were reported with ceftolozane/tazobactam + metronidazole versus 8 deaths (1.6%) with meropenem, but all TEAEs leading to death were judged to be unrelated to study treatment.

For both indications, most of the TEAEs were mild or moderate in intensity. The incidence of TEAEs of severe intensity was low and comparable across treatment groups (cUTI: 3.2% with ceftolozane/tazobactam vs. 1.9% with levofloxacin; cIAI: 7.5% with ceftolozane/tazobactam +

³⁵ One of the mechanisms of resistance in *P. aeruginosa* was the overexpression of an inducible chromosome-encoded AmpC β -lactamase, which can increase 100-1000 fold in the presence of certain β -lactams, particularly imipenem.

metronidazole vs. 5.6% with meropenem). In CXA-cUTI-10-04-05, the most commonly reported treatment-related AE by preferred term in the ceftolozane/tazobactam group was headache (1.9% with ceftolozane/tazobactam vs. 0.9% in the levofloxacin group). In CXA-cIAI-10-08-09, the most commonly reported treatment-related AE by preferred term in the ceftolozane/tazobactam + metronidazole group was diarrhoea (2.5% with ceftolozane/tazobactam + metronidazole vs. 2.4% in the meropenem group). Overall, across the 2 indications, the most commonly reported treatment-related AE by preferred term with ceftolozane/tazobactam were nausea (1.7% vs. 0.6% with comparators), diarrhoea (1.6% vs. 3.0%), headache (1.4% vs. 0.5%) and AST increased (1.0% vs. 0.7%).

For both indications, laboratory test results and vital signs did not raise any safety concerns.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of ceftolozane/tazobactam in the proposed usage for the treatment of complicated urinary tract infections (including pyelonephritis) and complicated intra-abdominal infections in combination with metronidazole are:

Efficacy results supported the use of ceftolozane/tazobactam in the treatment of cUTI, in terms of microbiological as well as clinical response. Intravenous ceftolozane/tazobactam 1.5 g every 8 h was non-inferior compared to intravenous levofloxacin 750mg once daily in the treatment of adult subjects with cUTI (including pyelonephritis) in terms of microbiological success rate at the TOC visit (7 days after the last dose of study drug) (ME at TOC population: microbiological success rate of 84.7% with ceftolozane/tazobactam vs. 75.4% with levofloxacin [treatment difference of 9.4%, 99% CI: 1.54, 17.12]; mMITT population: microbiological success rate of 78.6% vs. 69.9% [treatment difference of 8.7%, 99% CI: 0.77, 16.57]). Ceftolozane/tazobactam showed higher microbiological eradication rates at the EOT visit (within 24 hours after the last dose of study drug) compared to levofloxacin (ME at TOC population: microbiological success rate of 95.6% with ceftolozane/tazobactam vs. 84.4% with levofloxacin [treatment difference of 11.2%, 95% CI: 6.79, 15.66]; mMITT analysis population: microbiological success rate of 94.2% vs. 83.8% [treatment difference of 10.4%, 95% CI: 6.12, 14.74]). The rate of relapses at the LFU visit (28 to 35 days after the last dose of study drug) was low (28.6% with ceftolozane/tazobactam vs. 15.9% with levofloxacin), although the sustained microbiological eradication rate (microbiological response rate at the LFU visit) was lower in the ceftolozane/tazobactam group compared to the levofloxacin group (71.4% vs. 81.4%; treatment difference of -12.7% [95% CI: -27.84, 4.20]). Clinical cure rates were comparably high with both ceftolozane/tazobactam and levofloxacin at TOC visit (ME at TOC population: 95.9% with ceftolozane/tazobactam vs. 93.2% with levofloxacin; mMITT population: 92.0% vs. 88.6%) and at EOT visit (ME at TOC population: 97.4% vs. 96.6%; mMITT population: 94.2% vs. 92.3%). Sustained clinical response rates at the LFU visit were also comparably high between ceftolozane/tazobactam and levofloxacin groups (96.4% vs. 95.4%).

Efficacy results also supported the use of ceftolozane/tazobactam in combination with metronidazole in the treatment of cIAI, in terms of clinical as well as microbiological response. Intravenous ceftolozane/tazobactam 1.5g 8 hourly in combination with metronidazole 500 mg every 8 h was non-inferior to intravenous meropenem 1g 8 hourly in the treatment of adult subjects with cIAI in terms of clinical cure rate at the TOC visit (26 to 30 days after the first dose of study drug) (CE population: clinical cure rate of 94.1% with ceftolozane/tazobactam + metronidazole vs. 94.0% with meropenem [treatment difference of 0.0%, 99% CI: -4.16, 4.30]; ITT population: clinical cure rate of 83.8% vs. 85.8% [treatment difference of -2.2%, 99% CI: -7.95, 3.44]). These results were supported by clinical cure rates at the TOC visit in other analysis populations showing generally comparable clinical cure rates between the

ceftolozane/tazobactam + metronidazole group and the meropenem group (ME population: 94.2% vs. 94.7%; MITT population: 83.0% vs. 87.3%; Expanded ME population: 93.8% vs. 93.6%). Clinical cure rate at the EOT visit (within 24 hours after the last dose of study drug) was also comparable between ceftolozane/tazobactam + metronidazole and meropenem (treatment difference [ceftolozane/tazobactam + metronidazole minus meropenem] of -3.1% to -0.1%). Sustained clinical cure rates (at the LFU visit [38 to 45 days after the first dose of study drug]) were also comparable between the ceftolozane/tazobactam + metronidazole group and the meropenem group (treatment difference of -4.1% to 0.7%). In addition, microbiological success rates at the TOC visit were comparable between ceftolozane/tazobactam + metronidazole and meropenem (treatment difference of -3.4% to 0.9%).

Overall, there were no major safety concerns following use of Zerbaxa for proposed indications.

9.2. First round assessment of risks

The risks of ceftolozane/tazobactam in the proposed usage are:

- Gastrointestinal symptoms (nausea, diarrhoea)
- Headache
- Transaminases elevations

Overall, there were no major safety concerns following the use of ceftolozane/tazobactam for the proposed indications. The majority of AEs were mild to moderate in severity. For the cUTI indication, the most commonly reported treatment-related AE in the ceftolozane/tazobactam group was headache (1.9% with ceftolozane/tazobactam vs. 0.9% in the levofloxacin group). For the cIAI indication, the most commonly reported treatment-related AE in the ceftolozane/tazobactam + metronidazole group was diarrhoea (2.5% with ceftolozane/tazobactam + metronidazole vs. 2.4% in the meropenem group). Overall, across the 2 indications, the most commonly reported treatment-related AE by preferred term with ceftolozane/tazobactam was nausea (1.7% vs. 0.6% with comparators), diarrhoea (1.6% vs. 3.0%), headache (1.4% vs. 0.5%) and AST increased (1.0% vs. 0.7%).

Transaminase elevations are associated with β -lactam antibiotics. Safety results showed that the incidence of treatment-related ALT and AST elevations was low with ceftolozane/tazobactam. For the cUTI indication, the incidence of treatment-related raised ALT was 1.1% with ceftolozane/tazobactam vs. 0.7% with levofloxacin, while that of treatment-related raised AST of 1.3% vs. 0.7%. For the cIAI indication, the incidence of treatment-related raised ALT was 0.6% with ceftolozane/tazobactam + metronidazole vs. 0.6% with meropenem, while that for treatment-related raised AST was also 0.6% vs. 0.6%. None of these transaminase elevations were SAEs or led to study drug discontinuation except for 1 subject (in ceftolozane/tazobactam + metronidazole group in CXA-cIAI-10-08-09) where an SAE was reported for the preferred term of "hepatic enzyme increased". For both indications, incidences of significant transaminase elevations ($>3x$, $>5x$ or $>10x$ ULN) were low with both ceftolozane/tazobactam and comparators throughout the post-baseline study period (cUTI: $\leq 2.2\%$ with ceftolozane/tazobactam vs. $\leq 2.6\%$ with levofloxacin; cIAI: $\leq 1.1\%$ with ceftolozane/tazobactam + metronidazole vs. $\leq 1.6\%$ with meropenem).

For the indication of treatment of cUTI, the dosing regimen of ceftolozane/ tazobactam (1.5g 8 hourly) can be a disadvantage compared to the once a day dosing regimen of levofloxacin (750mg once daily). In addition the cUTI study was a non-inferiority study, which did not allow rigorous statistical conclusion regarding superiority of ceftolozane/tazobactam over levofloxacin, but only that it was non-inferior to levofloxacin with regards to the efficacy endpoints. However, it is noted that analyses of per-pathogen microbiologic response showed that ceftolozane/ tazobactam had greater microbiologic eradication rates compared to levofloxacin for gram-negative aerobes (87.6% vs. 75.0%). Consistent with findings in clinical

settings, gram-negative aerobes were the most commonly found baseline uropathogens in both treatment groups (94.7% in ceftolozane/tazobactam group and 96.3% in levofloxacin group). In addition, among subjects with ESBL-producing pathogens, microbiological response at the TOC visit was higher with ceftolozane/tazobactam compared to levofloxacin (mMITT population: 62.3% with ceftolozane/tazobactam vs. 37.0% with levofloxacin; ME population: 70.4% vs. 43.5%). Among subjects with baseline levofloxacin-resistant uropathogen, microbiological response at the TOC visit was also higher with ceftolozane/tazobactam compared to levofloxacin (65.2% vs. 42.2%; ME at TOC population).

In the cUTI study, efficacy results showed that although ceftolozane/ tazobactam had greater microbiologic eradication rates compared to levofloxacin for gram-negative aerobes (87.6% vs. 75.0%), it had lower microbiologic eradication rates compared to levofloxacin for gram-positive aerobes (33.3% vs. 80.0%). The sponsor had offered the rationale that the enterococcal isolates (gram-positive aerobes) were known to be inherently resistant to cephalosporins. In addition, it is noted that the majority of cUTI involves gram-negative rather than gram-positive aerobes.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of ceftolozane/tazobactam, given the proposed usage, is favourable.

Efficacy results supported the use of ceftolozane/tazobactam in the treatment of cUTI, and in the treatment of cIAI in combination with metronidazole, in terms of microbiological as well as clinical response. Compared to commonly used and recommended antibiotic regimen for the treatment of cUTI (levofloxacin) and of cIAI (meropenem), ceftolozane/tazobactam (monotherapy for cUTI, and plus metronidazole for cIAI) was found to be non-inferior for the respective indications. Safety results did not raise any major safety concerns and were generally comparable between ceftolozane/tazobactam and the comparators.

10. First round recommendation regarding authorisation

It is recommended that the application to register ceftolozane 1000 mg/tazobactam 500 mg for the treatment of adult patients with complicated urinary tract infections, including pyelonephritis, and the treatment of complicated intra-abdominal infections in combination with metronidazole, be approved. This is contingent upon satisfactory response by the sponsor to the comments and clinical questions.

11. Clinical questions

11.1. Pharmacokinetics

- Does the sponsor have further studies of the PK of ceftolozane as a single agent?

11.2. Pharmacodynamics

- Is there an analysis of the cardiovascular effects of the proposed combination after repeated dosing? The study evaluated single doses whereas the proposed clinical use is for repeated doses. The effect on the ECG in patients treated for therapeutic indications is therefore of further interest in addressing the cardiovascular effects of the combination.

11.3. Efficacy

- Please provide justification for the choice of inferiority margin of -10% for CXA-cUTI-10-04-05.

Rationale for question:

As described above, justification for the choice of non- inferiority margin of -10% for CXA-cUTI-10-04-05 was not described in the clinical study report or the SAP. It is noted by the evaluator that the addendum to the EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections states that for cUTI, the “suggested non-inferiority margin is -10%”, and that according to the FDA guidance for industry: complicated urinary tract infections and pyelonephritis- developing antimicrobial drugs for treatment, “In most cases, a noninferiority margin of 10 percent will be clinically acceptable and scientifically justified”. However, it is recommended that the sponsor provides explanation for the choice of non-inferiority margin as to whether it was based only on these guidelines, or other additional basis.

- Please provide details regarding the issues of GCP non-compliance at the 2 study sites in CXA-clAI-10-08-09, justification for the exclusion of the 23 randomised subjects enrolled at these 2 sites from the ITT population, as well as the timing at which the decision to exclude these subjects were made (e.g. before or after unblinding).

Rationale for question:

As described above, the above information was missing from the clinical study report. These details are needed in order to evaluate whether the exclusion of the subjects at these 2 sites from the ITT population is appropriate.

11.4. Safety

None

12. Second round evaluation

Overall, the sponsor has adequately addressed all the questions posed in the first round of evaluation. In this section on the evaluation of the sponsor’s responses to the questions posed in the first round of evaluation, each question will be re-stated for ease of reference, followed by the sponsor’s response and the evaluator’s response.

12.1. Pharmacokinetics

- *Does the sponsor have further studies of the PK of ceftolozane as a single agent?*

12.1.1. Sponsor’s Response

Three clinical studies were conducted with ceftolozane as a single agent. Study CXA-101-01 and CXA-101-02 were conducted in healthy volunteers and those with impaired renal function, respectively. Study CXA-101-03 was a Phase 2 study in patients with complicated urinary tract infection (cUTI). Pharmacokinetic data was collected in all 3 studies and incorporated into population pharmacokinetic models; this study data and POPPK information is presented in the Summary of Clinical Pharmacology. There are no further ongoing or planned PK studies with ceftolozane as a single agent.

12.1.2. Evaluator’s Response

The sponsor has not provided **additional** data on the PK of ceftolozane. Three studies were conducted CXA-101-01 in healthy volunteers, CXA-101-02 those with impaired renal function

and, CXA-101-03, a Phase 2 study, in patients with complicated urinary tract infection (cUTI). No further PK studies with ceftolozane as a single agent are planned.

12.2. Pharmacodynamics

- *Is there an analysis of the cardiovascular effects of the proposed combination after repeated dosing? The study evaluated single doses whereas the proposed clinical use is for repeated doses. The effect on the ECG in patients treated for therapeutic indications is therefore of further interest in addressing the cardiovascular effects of the combination.*

12.2.1. Sponsor's Response

A thorough QTc study was conducted in compliance with the FDA and EMA guidance documents on QT/QTc studies (DHHS 2005; CHMP 2005). QTc prolongation is a concentration-dependent adverse effect and as both products have a short half-life of <3 hours with no potential for or observed drug accumulation after repeat dosing, a single dose was considered appropriate for this study to evaluate the therapeutic and supra-therapeutic doses (Shah 2002).

In addition, cardiac safety was assessed during Phase 3 clinical trials by evaluating adverse events following repeat dosing. The frequency of adverse events in the Cardiac System Organ Class (SOC) were similar between treatment arms; Cardiac SOC events were reported in 3.2% (32/1015) and 3.6% (36/1032) for ceftolozane/tazobactam and comparators, respectively (SCS).

Additionally, antibiotics in the cephalosporin class have not been associated with cardiac toxicities and beta-lactam antibiotics have not been previously linked with QTc prolongation (Thompson 1993; Neu 1990; Owens 2008). Based on preclinical cardiac safety studies, the thorough QTC study demonstrating lack of effect on QTc at 3-times the therapeutic dose, low incidence of cardiac adverse events in the Phase 3 studies similar to comparators, and no past association with QTc toxicity with currently used beta-lactam antibiotics, the sponsor believes the risk of cardiac effect following multiple doses remains low.

12.2.2. Evaluator's Response

The sponsor has made the case that the thorough QTc study submitted following supra-therapeutic single doses is sufficient to evaluate the cardiovascular safety of Zerbaxa. This is based on consideration of the PK of both agents which have a short elimination half-life of <3 hours. Thus there is little potential for drug accumulation after repeat dosing. Furthermore no accumulation was observed in the repeat dosing studies conducted. Cardiac safety was assessed during Phase 3 clinical trials by evaluating adverse events following repeat dosing. The frequency of adverse events in the Cardiac System Organ Class (SOC) were similar between ceftolozane/tazobactam and comparative agents. This response is satisfactory.

12.3. Efficacy

- *Please provide justification for the choice of inferiority margin of -10% for CXA-cUTI-10-04-05.*

Rationale for question:

As described above, justification for the choice of non-inferiority margin of -10% for CXA-cUTI-10-04-05 was not described in the clinical study report or the SAP. It is noted by the evaluator that the addendum to the EMA guideline on the evaluation of medicinal products indicated for treatment of bacterial infections states that for cUTI, the "suggested non-inferiority margin is -10%", and that according to the FDA guidance for industry: complicated urinary tract infections and pyelonephritis- developing antimicrobial drugs for treatment, "In most cases, a noninferiority margin of 10 percent will be clinically acceptable and scientifically justified".

However, it is recommended that the sponsor provides explanation for the choice of non-inferiority margin as to whether it was based only on these guidelines, or other additional basis.

12.3.1. Sponsor's Response

To justify the non-inferiority margin of 10% for this study, an extensive search of the medical literature was conducted by the sponsor to find historical clinical trials to determine the activity of levofloxacin and placebo in subjects with cUTI.

The 95%-95% fixed margin approach was used to justify the non-inferiority margin. A meta-analysis using a non-iterative weighted DerSimonian and Laird random effects model was used to estimate the effect of levofloxacin versus placebo in the cUTI population based on data that were obtained from an extensive review of the medical literature (DerSimonian, 1986). The analysis showed that the estimated treatment difference of levofloxacin relative to placebo was 42.7%.

After discounting the estimated active control effect by 50% (MI = 21.4%) to account for heterogeneity across various historical studies included in the meta-analyses, the selected clinically relevant non-inferiority margin of 10% still ensures the preservation of 53.2% of the effect of levofloxacin.

Details of the justification for the non-inferiority margin for this study are provided.

12.3.2. Evaluator's Response

The sponsor provided justification for the choice of non-inferiority (NI) margin of -10% for CXA-cUTI-10-04-05. The fixed margin approach (using 95% confidence interval) was used to justify the NI margin. A non-iterative weighted DerSimonian and Laird random effect model was used to estimate the active control effect (levofloxacin) versus placebo infusion in the cUTI population based on data that were obtained from a review of the medical literature. The analysis showed that the estimated treatment difference of levofloxacin relative to placebo was 42.7%. After discounting the estimated active control effect by 50% to account for heterogeneity across various historical studies included in the meta-analyses ($M_1=21.4\%$; considered to represent a very conservative estimate of the benefit of active drug over placebo), the clinically relevant non-inferiority margin (M_2) of 10% was estimated to still be able to ensure the preservation of approximately 53.2% of the effect of levofloxacin. The rationale for the non-inferiority margin is generally consistent with the relevant FDA, EMA and ICH guidelines on non-inferiority statistical analyses. The sponsor's response to this question has not resulted in any changes to the conclusions of the first round of evaluation.

- *Please provide details regarding the issues of GCP non-compliance at the 2 study sites in CXA-clAI-10-08-09, justification for the exclusion of the 23 randomised subjects enrolled at these 2 sites from the ITT population, as well as the timing at which the decision to exclude these subjects were made (e.g. before or after unblinding).*

Rationale for question:

As described above, the above information was missing from the clinical study report. These details are needed in order to evaluate whether the exclusion of the subjects at these 2 sites from the ITT population is appropriate.

12.3.3. Sponsor's Response

Two sites (Site 1008-4024 [n = 7] and Site 1009-4227 [n = 16]) were closed due to concerns with GCP noncompliance and potential risk to data integrity. The decision to exclude data from these 2 sites was made prior to unblinding according to the Statistical Analysis Plan.

Site 1009-4227 (n=16) in Argentina was closed due to significant scientific misconduct. On 07 May 2013, Cubist sent a letter to the FDA and the Argentinian Ministry of Health regarding site misconduct and closure.

Site 1008-4024 (n=7) in the US was closed due to several deficiencies related to informed consent not being properly obtained or documented, failure to follow the Outpatient Parenteral Antimicrobial Therapy (OPAT) plan, issues with drug monitoring and accountability records, inadequate source documentation, missing essential documentation, and lack of investigator oversight. On 21 May 2013, Cubist sent a letter to FDA regarding site noncompliance and closure.

Data from the 2 sites that were closed were excluded from all efficacy analyses; however, in order to identify and explore the impact of the exclusion of the 2 sites that were closed, a sensitivity analysis in the ITT population including all subjects from the 2 sites was conducted. Based on the sensitivity analysis, exclusion of data from these 2 sites had no impact on the overall outcome of the trial. A listing summarising the 2 sites and excluded subjects is provided.

Of these subjects 11 were in the ceftolozane/tazobactam + metronidazole arm and 12 were in the meropenem arm. Twenty-two of the 23 subjects excluded from the ITT population received study drug and therefore were included in the Safety population. This analysis is provided.

12.3.4. Evaluator's Response

The sponsor provided additional information on the exclusion of the 23 randomised subjects enrolled at these 2 sites from the ITT population. The 2 sites (Site 1008-4024 [n = 7] and Site 1009-4227 [n = 16]) were closed due to concerns with GCP non-compliance and potential risk to data integrity. Site 1009-4227 (n=16) in Argentina was closed due to significant scientific misconduct. Site 1008-4024 (n=7) in the US was closed due to several deficiencies related to informed consent not being properly obtained or documented, failure to follow the Outpatient Parenteral Antimicrobial Therapy plan, issues with drug monitoring and accountability records, inadequate source documentation, missing essential documentation, and lack of investigator oversight. The decision to exclude data from these 2 sites was made prior to unblinding. An additional sensitivity analysis in the ITT population including all subjects from the 2 sites was conducted in order to explore the impact of the exclusion of the 2 sites that were closed. The sensitive analysis yielded similar efficacy results, suggesting that the exclusion of data from these 2 sites had no impact on the overall outcome of the trial. The sponsor's response to this question has not resulted in any changes to the conclusions of the first round of evaluation.

12.4. Safety

None.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ceftolozane/tazobactam in the proposed usage are unchanged from those identified in the first round.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of ceftolozane/tazobactam in the proposed usage are unchanged from those identified in the first round.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of ceftolozane/tazobactam, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

It is recommended that the application to register ceftolozane 1000 mg/tazobactam 500 mg for the treatment of adult patients with complicated urinary tract infections, including pyelonephritis, and the treatment of complicated intra-abdominal infections in combination with metronidazole, be approved.

15. Population pharmacokinetics

15.1. Introduction

The population pharmacokinetic evaluation has been undertaken to replicate the key analysis of the population PK Study CUBI-PCS-100 and to perform critical appraisals of the study reports for population PK Study CUBI-PCS-100 and the PK/PD Study CXA-101-PH-003.

15.1.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Four population PK analyses. One was supplied for evaluation and the remaining three were supplied for information.
- One population PK/PD analysis and simulation study for evaluation.

15.2. Pharmacokinetics

15.2.1. Summary of previously described PK

Ceftolozane C_{max} and AUC are dose proportional for single doses in the range 250 mg to 3 g and at steady state in the range 500 mg to 3 g q8h. There was no accumulation with multiple doses. There was no PK interaction between ceftolozane and tazobactam. Elimination t_{1/2} is in the range 2 to 3 hours and is independent of dose. Plasma protein binding of ceftolozane is in the range 16% to 21% and for tazobactam is 30%. Apparent volume of distribution is approximately 12 to 17 L for ceftolozane and 14 to 19 L for tazobactam. Approximately 99% of the administered dose of ceftolozane is excreted unchanged in the urine. Values for renal clearance of the drug from plasma (CLR) were similar to total body clearance from the plasma (CL) and to glomerular filtration rate for the unbound fraction, suggesting that ceftolozane is predominantly eliminated by glomerular filtration and that tubular secretion-related drug interactions observed with other antibacterials are not expected with ceftolozane. Tazobactam is eliminated primarily by renal excretion with >80% as unchanged drug through glomerular filtration and tubular secretion and the remaining fraction as the single M1 metabolite (which is pharmacologically inactive). Inhibitors of OAT1/OAT3 (e.g. probenecid) increase the t_{1/2} of tazobactam.

The Sponsor has explored the PK of ceftolozane in subjects with a range of renal impairment: normal; mild, moderate and severe renal impairment; and end stage renal disease (ESRD). Based on these data, relative to ceftolozane/tazobactam exposures in subjects with normal renal function (CLCR ≥90 mL/min), there were slightly increased exposures observed in subjects with mild renal impairment (CLCR >50 to 89 mL/min) that were not clinically relevant and exposures that were increased approximately 2- to 2.5-fold and 3- to 5-fold in subjects with moderate (CLCR 30 to 50 mL/min) and severe (CLCR 15 to 29 mL/min) renal impairment, respectively. The Sponsor has used these data to calculate the dose recommendations in patents with renal impairment or ESRD. The population pharmacokinetic analyses were used to support these recommendations which appear to have been derived from the phase 1 studies.

15.2.2. Studies providing PK data

Table 4 shows submitted population PK/PD studies.

Table 4: Submitted population PK/PD studies.

| Population PKPD Study | Studies contributing Data | Study Population | Number of Subjects |
|-----------------------|---------------------------|---|--------------------|
| Study CUBI-PCS-100 | CXA-101-01 | Healthy | 48 |
| | CXA-201-01 | Healthy | 48 |
| | CXA-QT-10-02 | Healthy | 51 |
| | CXA-ELF-10-03 | Healthy | 25 |
| | CXA-MD-11-07 | Healthy | 12 |
| | CXA-101-02 | Healthy /mild renal impairment | 12 |
| | CXA-201-02 | Healthy and mild to moderate renal impairment | 24 |
| | CXA-REN-11-01 | Severe renal impairment | 6 |
| | CXA-IAI-10-01 | Patients: UTI | 77 |
| | CXA-101-03 | Patients: intra-abdominal infection | 73 |

15.2.3. Description of the population PK studies

15.2.3.1. Study CUBI-PCS-100

15.2.3.1.1. Objective of the analysis

- To enrich the previously developed population PK models for ceftolozane/tazobactam by including additional PK data from the following studies:
 - Phase 1 studies in healthy subjects (CXA-101-01, CXA-QT-10-02, CXA-ELF-10-03, CXA-MD-11-07)
 - Phase 1 studies in special populations (CXA-101-02, CXA-REN-11-01)
 - Phase 2 study in patients (CXA-IAI-10-01)
- To determine sources of variability in PK parameters of ceftolozane/tazobactam, and identify intrinsic and extrinsic clinically relevant covariates, if any
- To use the developed population PK model to derive individual exposure values of ceftolozane/tazobactam in special populations (renal impairment, patients with bacterial infections etc.), and use estimated exposure to support any dosing modifications for these special populations

15.2.3.1.2. Data

15.2.3.1.2.1. Ceftolozane data

The data were obtained from ten clinical studies. There were eight Phase 1 studies, five of which were performed in healthy volunteers and three in subjects with various degrees of renal impairment (normal, mild, moderate, severe and end stage renal disease [ESRD]). There were two Phase 2 studies conducted in subjects with urinary tract or intra-abdominal infections. There were 376 subjects: 212 (56.4%) male and 164 (43.6%) female. The study population were predominantly Caucasian: 332 (88.3%) subjects. There were 150 (39.9%) subjects with infection. There were 121 (32.2%) subjects with renal impairment. The age range was 18 to 86 years, height was 149 to 190 cm, weight 42.9 to 173 kg, BMI 17.2 to 56.3 kg/m², and CLCR 19.1 to 309 mL/min.

There were 5048 ceftolozane plasma concentrations included in the dataset. There were 540 (9.45%) observations excluded because they were BLQ and 127 (2.22%) were excluded for other reasons.

15.2.3.1.2.2. Tazobactam data

The data were obtained from the same studies listed. There were 243 subjects: 139 (57.2%) male and 104 (42.8%) female. The study population were also predominantly Caucasian: 212 (87.2%) subjects. There were 77 (31.7%) subjects with infection. There were 58 (23.9%) subjects with renal impairment. The age range was 18 to 86 years, height was 149 to 190 cm, weight 49.0 to 145 kg, BMI 18.4 to 50.8 kg/m², and CLCR 19.1 to 309 mL/min.

There were 2683 ceftolozane plasma concentrations included in the dataset. There were 1475 (34.7%) observations excluded because they were BLQ and 91 (2.14%) were excluded for other reasons.

15.2.3.1.3. Methods

The software used for the population PK analysis was Phoenix Non-Linear Mixed Effects (NLME) Version 1.2. Dataset preparation and some exploratory analyses were performed using S-PLUS v8.2, R (2.15.0) and Microsoft Office Excel 2003.

The estimation was performed using extended least squares first order conditional estimation (FOCE-ELS). This estimation method is similar to FOCE with INTERACTION as used in NONMEM.

Plasma samples that were BLQ were excluded from the analysis. There was no imputation of missing data.

The structural model was taken from previously performed population PK analyses of ceftazolin and tazobactam. For both drugs these were two compartment models parameterised as clearance. The Omega matrix was diagonal. Inter-individual variability was modelled as exponential for CL and Vc, but was not estimated for Q or Vp.

The covariate model was developed by using plots of ETAs for CL and V against each potential covariate. A forward inclusion, backward exclusion approach was used with a p-value of <0.01 for inclusion and ≥ 0.001 for exclusion. Continuous variables were added to the model centralised at the median and categorical variables were added using an exponential factor relative to the reference category.

The final models were evaluated using goodness of fit plots, a bootstrap approach with 1000 replicates and visual predictive checks.

15.2.3.1.4. Results

15.2.3.1.4.1. Ceftazolin

The base model was adopted from previous studies. The parameters were estimated with precision with the typical value (RSE%) for CL being 5.33 (2.33) L/h and Vc being 13.3 (2.47) L. Inter-individual and residual errors were estimated with excellent precision. However, the plot of DV versus PRED indicated a tendency to underestimate some values.

The plots of continuous variables versus individual ETAs indicated the primary covariate for CL was likely to be renal function. This was also supported by the boxplots of categorical variables versus individual ETAs. The final covariate model included the effects of renal function (as measured by CRCL) and infection on CL, and weight and infection on Vc. The bootstrap validation resulted in values for the parameters and error terms that were essentially the same as the final model. The diagnostic plots, particularly that of DV versus PRED, demonstrated an improved fit for the final model in comparison with the base model. The visual predictive check indicated a good predictive ability for the model except for the 1000 mg dose level, where the model tended to under-predict plasma concentrations mid-dose.

The primary effect on CL was renal function, and the presence of infection had only a minor effect on CL. These effects were more apparent when observing the effects of renal function and infection on AUC and Cmax. Renal impairment significantly increased both AUC and Cmax, whereas the decrease in Cmax with infection did not appear to be significant.

15.2.3.1.4.2. Tazobactam

The structural model for tazobactam was also derived from previous studies and was the same as that for ceftazolin. The parameters were estimated with precision with the typical value (RSE%) for CL being 17.1 (3.90) L/h and Vc being 15.3 (3.91) L. Inter-individual and residual errors were estimated with excellent precision. However, the plot of DV versus PRED, in common with that for ceftazolin, indicated a tendency to underestimate some values.

The plots of continuous variables versus individual ETAs indicated effects of renal function on CL and weight on Vc. This was also supported by the boxplots of categorical variables versus individual ETAs. The final covariate model included the effects of renal function (as measured by CRCL) on CL, and infection on Vc. The bootstrap validation resulted in values for the parameters and error terms that were essentially the same as the final model. The diagnostic plots demonstrated an improved fit for the final model in comparison with the base model plot of DV versus PRED still indicated some tendency to under-predict. The visual predictive check indicated an acceptable ability for the model to predict plasma concentrations.

The effect of renal function on CL was clinically significant. The effects of renal function were also apparent on AUC and Cmax. Renal impairment significantly increased both AUC and Cmax. The effects of infection did not appear to be clinically significant.

15.2.3.1.5. Validations

15.2.3.1.5.1. Validation Method

The models were evaluated in Phoenix 64 using NLME 1.2. The estimation method was FOCE-ELS. The population PK model and conditions for the estimations were the same as those described in the model description files supplied by the sponsor. The same input files, as used and provided by the Sponsor, were also used in the evaluation estimations.

15.2.3.1.5.2. Validation Results: Ceftolozane

For the base model for ceftolozane, the evaluation estimation provided the same parameter and error estimates as those provided by the Sponsor. The model diagnostic plots indicate a similar fit for the model to the data. These plots also indicate an appropriate specification for the residual error model.

For the final population PK model, the estimates of the parameter and error estimates were similar to those of the Sponsor. The estimates for the covariate effects of CRCL on CL and weight on Vc were similar, and there was no significant difference compared to the Sponsor's estimates. However, the estimates for the covariate effects of infection on CL and Vc were significantly lower for the evaluation compared to those of the Sponsor. However, if these covariate effects are converted from the exponent, they become similar to the Sponsor's estimates. Hence the differences appear to be in the way the results are reported. The Sponsor has reported the results in a manner that assist the reader in interpreting the results. The model diagnostic plots indicate a similar fit for the model to the data compared to those from the Sponsor's model.

15.2.3.1.5.3. Validation Results: Tazobactam

For the base model for tazobactam, the evaluation estimation provided very minor differences in parameter and error estimates compared to those provided by the Sponsor. The model diagnostic plots indicate a similar fit for the model to the data. These plots also indicate an appropriate specification for the residual error model.

For the final population PK model, the estimates of the parameter and error estimates were similar to those of the Sponsor. The estimates for the covariate effect of CRCL on CL was similar, and there was no significant difference compared to the Sponsor's estimates. However, the estimates for the covariate effects of infection on Vc was significantly lower for the evaluation compared to those of the Sponsor. However, if that covariate effect is converted from the exponent, it becomes similar to the Sponsor's estimate. Hence the difference appears to be in the way the results are reported. The Sponsor has reported the results in a manner that assist the reader in interpreting the results. The model diagnostic plots indicate a similar fit for the model to the data compared to those from the Sponsor's model.

15.2.3.1.5.4. Comparison of submitted results and validation results

The results of the evaluation and the Sponsor were in agreement. Although the same software, estimation methods, models and initial estimates were used in the two analyses, minor differences in parameter estimates may be due to differences in computer processors.

15.2.4. Evaluator's overall conclusions on the population pharmacokinetic analysis

The modelling process was conducted and reported in accordance with the Guideline on Reporting the Results of population Pharmacokinetic Analyses CHMP/EWP/185990/06.

The base structural models were adopted from previous studies. This is an acceptable strategy because the phase 1 data are rich (i.e. many observations per subjects) and are well suited to

describing the structural model. The error models had been developed in previous population PK studies, using mostly the same data, and were well supported. The residual error models were also adopted from previous population PK models, but were also supported by the model diagnostic plots (from the Sponsor's analysis and also from the Evaluator's analysis).

The covariate models were developed using all the available covariate data. The covariate model building processes were rigorous. The final models were supported by the goodness of fit plots, the bootstrap analyses and the VPCs. The covariates that remained in the final model were consistent with the known pharmacokinetic characteristics of ceftolozane and tazobactam.

The modelling process supports the proposed dosing regimen. However, these dosing recommendations were not derived from the population PK models. There were no simulations of dosing regimens provided in the reports.

15.3. Pharmacodynamics

15.3.1. Study CXA-101-PH-003

15.3.1.1. Objective of the analysis

To evaluate the probability of pharmacodynamic target attainment for the optimal dosage regimen of ceftolozane in subjects with normal renal functions based on the MIC distributions of ceftolozane and ceftolozane in combination with β -lactamase inhibitor, tazobactam for various pathogens from 2008 US surveillance study.

15.3.1.2. Data

The bacteriological data were obtained from US surveillance data from 2008. The data were obtained from a central laboratory, Eurofins Medinet. The isolates were randomly selected for the study so that they can represent the current real antibiogram in the US hospitals. The MICs of ceftolozane alone and in combination with tazobactam (4 μ g/mL) were determined for the isolates of the following organisms:

- Streptococcus pneumoniae (N=276)
- Streptococcus pyogenes (N=42)
- Streptococcus agalactiae (N=18)
- Pseudomonas aeruginosa (N=914)
- Haemophilus influenza (N=95)
- Acinetobacter species (N=238)
- Escherichia coli (N=721)
- Klebsiella pneumoniae (N=798)
- Enterobacter cloacae (N=266)
- Citrobacter species (N=158),
- Proteus mirabilis (N=352)
- Serratia marcescens (N=256)
- All Enterobacteriaceae (N=2551).

15.3.1.3. Methods

The population PK model was taken from Study CXA-101-PH-002. The final model was a two compartment model, parameterized as CL with an effect of CRCL on CL. The estimates of the population PK parameters and error terms from the model were used to perform Monte Carlo simulations in order to predict %T>MIC at different dose levels and in subjects with different degrees of renal impairment. The simulation was performed using NONMEM with 4000 replicates. Plasma concentrations were simulated over an 8 hour interval at steady state dosing of ceftolozane 1000 mg q8h in subjects with normal renal function. The visual predictive check for the model indicated a good predictive ability for this time period in the same subject group. The ceftolozane concentration target was randomly assigned to one of the seven MIC values (1, 2, 4, 8, 16, 32, and 64 µg/mL) according to the probability of MIC distribution of ceftolozane for various organisms.

15.3.1.4. Results

Acinetobacter and Enterobacter cloacae susceptibilities were poor for ceftolozane alone. However, in combination with tazobactam 4 µg/mL susceptibilities were increased including those for Acinetobacter and for Enterobacter cloacae.

The aim for a betalactam antibiotic, such as ceftolozane, is to maintain the plasma concentration above MIC for 40% to 70% of the time. The Sponsor has nominated a target attainment for free drug T>MIC of 50% for >90% of isolates as the PD outcome of interest. For ceftolozane alone this target was attained for Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Pseudomonas aeruginosa, Haemophilus influenzae, Escherichia coli, Proteus mirabilis, and Serratia marcescens. The target was not achieved for Acinetobacter species, Klebsiella pneumoniae, Enterobacter cloacae, and Citrobacter species. In combination with tazobactam, this target was attained for Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Pseudomonas aeruginosa, Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae, Citrobacter species, Proteus mirabilis, and Serratia marcescens. The target was not achieved for Acinetobacter species and Enterobacter cloacae.

15.3.2. Evaluator's overall conclusions on the PK / PD analysis

The PK / PD data support a dose regimen of 1000 mg q8h for the treatment of common streptococcal and gram negative infections, with the exception of Acinetobacter species and Enterobacter cloacae.

The methodology of the PK / PD study was sound. The PK data were simulated from the results of a population PK study that had acceptable predictive ability at the dose level used in the study. The bacteriological data were obtained as a representative population in the US hospital system. This would be comparable to the Australian hospital system. The modelling and simulation was performed using appropriate methods.

However, the data do not support a dose regimen using a lower dose of ceftolozane/tazobactam. Specifically, no data were provided that support a dose regimen of 500 mg q8h.

15.4. Dosage selection for the pivotal studies

Not evaluated.

15.5. Efficacy

Not evaluated.

15.6. Safety

Not evaluated.

15.7. First round benefit-risk assessment

15.7.1. First round assessment of benefits

The data were supportive for the efficacy of Zerbaxa (ceftolozane sulfate/tazobactam sodium) at a dose of 1000 mg q8h for the treatment of common streptococcal and gram negative infections, with the exception of Acinetobacter species and Enterobacter cloacae.

The population PK data support dose adjustment in patients with moderate or severe renal impairment, or with ESRD. However, the population PK data were not used to simulate dosing regimens in these populations.

The PK/PD data do not support the sponsor's recommendation for a dose of ceftolozane 500 mg q8h.

15.7.2. First round assessment of risks

No new risks were identified in the population PK or PK/PD data.

15.7.3. First round assessment of benefit-risk balance

The evaluator is not in a position to comment on the overall benefit-risk balance.

15.8. First round recommendation regarding authorisation

The evaluator is not in a position to provide a recommendation regarding authorisation.

15.9. Clinical questions

- Does the sponsor have any PK/PD data with regard the proposed 500 mg q8h dosing regimen?

15.10. Second round evaluation

The sponsor has provided a report of an additional simulation study (Study ICPD 00319). The objective of the study was to provide support for:

- Recommendations for in vitro susceptibility test interpretive criteria for ceftolozane/tazobactam against Pseudomonas aeruginosa
- Selected ceftolozane/tazobactam dosing regimens by renal function category

The renal function categories were:

- High normal renal function (>150 to ≤200 mL/min)
- Normal renal function (>90 to ≤150 mL/min)
- Mild renal impairment (>50 to ≤ 90 mL/min)
- Moderate renal impairment (≥29 to ≤ 50 mL/min)
- Severe renal impairment (≥15 to <29 mL/min)

The PK model used to generate the PK profiles was derived from Study CUBI-PCS-100. Monte Carlo simulation was used to generate 1000 PK profiles in each renal function group. Renal function was randomly sampled from uniform distributions. BW was randomly sampled from a log-normal distribution. The dose ranges used were 250 mg to 2000 mg, administered every 8

h. The plasma concentration profiles were compared with the profile of MICs for North American strains of *P. aeruginosa*.

The results support the dose recommendations for patients with renal impairment in the PI document. The following doses were supported by the results:

- In patients with high normal renal function: 1000 mg ceftozolane/500 mg tazobactam q8h
- In patients with normal renal function: 1000 mg ceftozolane/500 mg tazobactam q8h
- In patients with mild renal impairment: 1000 mg ceftozolane/500mg tazobactam q8h
- In patients with moderate renal impairment: 500 mg ceftozolane/250 mg tazobactam q8h
- In patients with severe renal impairment: 250 mg ceftozolane/125mg tazobactam q8h

The methodology used in the simulation study was appropriate. Specifically, the population pharmacokinetic model was previously evaluated and considered appropriate. The methods used to simulate and to determine the likely effectiveness were also appropriate. The new data supports the modified dosing strategy in patients with renal impairment.

15.11. Second round benefit-risk assessment

15.11.1. Second round assessment of benefits

The submitted data support the proposed dosing regimens for Zerbaxa (ceftolozane sulfate/tazobactam sodium).

15.11.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Zerbaxa (ceftolozane sulfate/tazobactam sodium) in the proposed usage are unchanged from those identified in the first round evaluation.

15.11.3. Second round assessment of benefit-risk balance

The population PK evaluator is not in a position to provide an assessment of risk-benefit balance.

15.12. Second round recommendation regarding authorisation

The population PK evaluator has no objections to authorisation arising from the evaluation of the population PK/PD data.

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