CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 206829
Priority or Standard	Priority
Submit Date(s)	April 21, 2014
Received Date(s)	April 21, 2014
PDUFA Goal Date	December 21, 2014
Division / Office	DAIP/OAP
Reviewer Names	Maria Allende, M.D., Hala Shamsuddin, M.D.
Review Completion Date	September 16, 2014
Established Name	Ceftolozane/tazobactam
(Proposed) Trade Name	Zerbaxa
Therapeutic Class	Cephalosporin plus Beta-lactamase inhibitor
Applicant	Cubist Pharmaceuticals, Inc.
Formulations	Intravenous
Dosing Regimen	1.5 g (1g of ceftolozane plus 0.5 g of tazobactam) every 8 hours
Indications	Complicated Urinary Tract Infections and Complicated Intra-abdominal Infections
Intended Population	Adults, ages 18 years and older

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommendation is to approve ceftolozane/tazobactam (Zerbaxa) for the treatment of complicated urinary tract infection, including pyelonephritis, and for the treatment of complicated intra-abdominal infection in combination with metronidazole.

The evidence submitted from the two adequate and well-controlled studies in complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI), using a dose of 1.5 g every 8 hours, show that ceftolozane/tazobactam met the pre-specified non-inferiority margin for the primary endpoint for each trial, with respect to the comparators (levofloxacin for the cUTI indication and meropenem for the cIAI indication).

This evidence, as well as the safety review of the clinical data submitted, support that ceftolozane/tazobactam should be approved to be used alone at the recommended dosage for the indication of cUTI and in combination with metronidazole 500 mg every 8 hours for the indication of cIAI. My recommendation is to approve it for both indications, with modifications to the applicant's proposed label.

1.2 Risk Benefit Assessment

The overall risk benefit assessment of ceftolozane/tazobactam is favorable for both the cUTI and cIAI indications.

In the cUTI indication, ceftolozane/tazobactam 1.5 gm IV every 8 hours for 7 days was non-inferior to levofloxacin 750 mg IV daily for 7 days for the primary endpoint of composite clinical and microbiological cure at the Test-of-Cure (TOC) visit (7 +/-2 days after the last dose) in the mMITT population (randomized subjects who received any amount of drug and who had at least one qualifying uropathogen at baseline). Composite cure rates were 77% and 69% for ceftolozane/tazobactam and levofloxacin, respectively (95% CI 2.3, 14.6). The 99% confidence interval for the difference in composite cure (0.36, 14.5) suggested that ceftolozane/tazobactam was superior to levofloxacin. However, the proportion of isolates that were resistant to levofloxacin at baseline was considerably higher in the levofloxacin arm compared to the proportion of isolates that were resistant to ceftolozane/tazobactam at baseline in the ceftolozane/tazobactam arm (28% vs 3%), indicating that 97% of subjects in the ceftolozane/tazobactam arm received an antimicrobial to which the organism was susceptible, and 72% of subjects in the levofloxacin arm received an antimicrobial to which the organism was susceptible. The conclusion of superiority was driven by the superiority of ceftolozane/tazobactam in the subset of subjects with levofloxacin resistant pathogens at baseline. Among subjects with baseline levofloxacin susceptible organisms, ceftolozane/tazobactam was non-inferior to levofloxacin for the composite cure and also non-inferior for clinical cure and microbiologic cures individually. The frequency and nature of adverse events were similar in the two treatment arms. The cUTI study protocol did not require testing for *Clostridium difficile* in the event of diarrhea. The rate of *C. difficile*-associated diarrhea was low, but is likely underestimated in both treatment arms.

In the cIAI indication, ceftolozane/tazobactam was marginally non-inferior to the comparator for the primary endpoint of clinical cure rates within a 10% margin (the lower bound of the 95% confidence interval was slightly greater than -10).

The safety profile was similar to that of the active comparators although slightly higher rates of adverse events were observed in the ceftolozane/tazobactam arm. The safety profile reflected the common events associated with the use of cephalosporins. The most common adverse events (occurring in more than 1% of subjects in the integrated pivotal studies) were nausea, diarrhea, vomiting, headache, pyrexia, constipation, insomnia, transaminases elevation, hypertension and hypokalemia.

Serious adverse events identified as related to ceftolozane/tazobactam were cases of *C. difficile* diarrhea or pseudomembranous colitis, which occurred at low rates, similar to those of the comparators. Regarding specific class-related toxicities, there was a low incidence of Coombs reaction conversion from negative to positive, and in all cases, no manifestation of hemolytic anemia was observed. There were no cases of anaphylactic shock or serious hypersensitivity reactions in the ceftolozane/tazobactam arm in clinical studies. Rashes were observed at a low frequency, compared to that of the comparators. Transaminases elevations were observed and were transient; however, no indication of drug-induced liver injury was identified as measured by subjects meeting criteria of Hy's law after initiation of study drug in the phase 3 studies. Adverse events indicative of renal impairment were infrequent overall; however, more subjects in the ceftolozane/tazobactam arm discontinued the drug due to worsening renal function. Although it is difficult to infer these events as causally related to the drug, the renal system is a target organ for toxicity in nonclinical studies and the only pathway of drug elimination, and renal toxicity is likely to be drug related.

In the cIAI indication, ceftolozane/tazobactam treatment was associated with relatively higher rates of infections and complications of the infection such as thrombocytosis, deep venous thrombosis events, and an overall higher number of arrhythmias and a non-statistically significant higher rate of deaths (1% difference). These are known complications of intra-abdominal infections and surgery in subjects with predisposing chronic conditions, mainly cardiac and pulmonary diseases. They likely reflect the severity of the underlying infection in patients with other co-morbidities. However, relatively lower efficacy of ceftolozane/tazobactam is suggested by the higher number of infection complications observed and cannot be ruled out as a contributing factor to the imbalance observed in these events.

There is insufficient information to determine whether the relatively lower efficacy of ceftolozane/tazobactam in the cIAI indication, which was not observed in the cUTI indication, could be due to a potential suboptimal dose of the drug for the intra-abdominal site of infection. This possibility cannot be excluded, since only one dose was studied in the clinical program for this indication.

These trends were not observed in the cUTI indication, where the drug showed higher rates of efficacy and the study population did not have the additional morbidity associated with surgical procedures. The incidence of thromboembolic events is higher in the ceftolozane/tazobactam plus metronidazole arm in the cIAI study and it seems higher than what is usually reported for post-surgery

thromboembolic events (AHQR and CDC reported rates), although there are several limitations about this type of events comparison. I am concerned about a potential signal of increased venous and arterial thromboembolic events in the ceftolozane/tazobactam plus metronidazole arm of the cIAI indication, but I cannot definitely attribute it to the drug because there are too many confounding risk factors and because these events were not observed in higher frequency in the cUTI study. This uncertainty should not preclude approval because the drug will be used for the treatment of life-threatening infections.

From the subgroup analyses in the cIAI indication, there appeared to be a higher incidence of adverse events in older subjects with bowel infections compared with subjects with other primary sites of infection, and among subjects with an APACHE II score ≥10 compared with subjects with a score <10 in both the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, but slightly more frequently observed in the ceftolozane/tazobactam plus metronidazole arm. There were several confounding risk factors in the more severely ill patient population that characterizes the cIAI indication, particularly in older patients, and it is not possible to evaluate the drug contribution to the causality of these events. Compared to the cUTI patient population, the cIAI subjects received a higher number of concomitant medications and had surgical procedures, which increased the likelihood for more frequent and serious adverse events.

No formal dose-ranging studies were conducted in the clinical development program. Only one dose, 1.5g every 8 hours, was studied in clinical studies, with limited human pharmacokinetic and pharmacodynamic data. The relatively lower efficacy trend observed in the cIAI trial raises the possibility that a higher dose could potentially be more effective, particularly in older patients. Studies exploring the safety and bioavailability of study drug in the intra-abdominal organs, using a higher dose and two or more age cohorts, including the elderly, would be very informative, and I would recommend them to the applicant, although not necessarily as a post-marketing commitment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None. Adverse reactions associated with ceftolozane/tazobactam can be adequately addressed in labeling.

1.4 Recommendations for Postmarket Requirements and Commitments

Post-marketing requirements recommendations include:

- Surveillance for developing resistance to ceftolozane/tazobactam over a five-year period
- Pediatric Research and Equity Act (PREA) requirements:
  The Division, with concurrence from the Pediatric Review Committee, agreed to the initial Pediatric Study Plan submitted by the applicant on September 18, 2013. Cubist will conduct the following three clinical trials in children aged 0 to 17 years to support the use of ceftolozane/tazobactam in the indications of cUTI and cIAI in pediatric patients:
    - **Study 1**: A single dose, open-label, multicenter, non comparative study to assess the pharmacokinetics (PK) of ceftolozane/tazobactam in children <18 years of age.

- **Study 2**: A double-blind, multicenter, randomized comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years of age with cUTI.
- **Study 3:** Randomized, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared with that of meropenem in hospitalized children from birth to <18 years of age with cIAI.

The target date for submission of the complete pediatric application is June, 2021. For more details, please refer to section 7.6.3.

Recommendations for post-marketing commitment include:

- A dose-ranging safety and efficacy study in patients older than 65 years of age for the intra-abdominal indication to include a higher dose arm.

2 Introduction and Regulatory Background

2.1 Product Information

Ceftolozane/tazobactam (CXA 201) is a combination product containing a 3′-aminopyrazolium cephalosporin, ceftolozane, and tazobactam, a β-lactamase inhibitor (BLI), developed as an option for treatment of serious infections caused by Gram negative bacteria including multi-drug resistant *P. aeruginosa* and also β-lactam-resistant *Enterobacteriaceae.*

Ceftolozane is a new molecular entity (NME) in the cephalosporins class and has never been marketed before. Like other members of the cephalosporin class, ceftolozane exerts its bactericidal activity by inhibiting essential penicillin-binding proteins (PBPs), resulting in inhibition of cell wall synthesis and subsequent cell death. Ceftolozane is a PBP3 inhibitor, and shows affinities for all the essential PBPs (1b, 1c, and 3) in *P. aeruginosa*.

Tazobactam is a derivative of the penicillin nucleus and it is chemically a penicillanic acid sulfone. Tazobactam is an irreversible inhibitor of β-lactamases and can bind covalently to chromosomal and plasmid-mediated bacterial β-lactamases. Tazobactam is not approved as a single agent; it is available as a component of a combination product with piperacillin, an anti-pseudomonal penicillin (a ureidopenicillin), in a ratio of 1:8. This product has been approved and used in the United States since October 22, 1993 (Zosyn®).

2.2 Tables of Currently Available Treatments for Proposed Indications

The following tables below show the list of antibacterial agents that are currently approved in the United States for the treatment of infections caused by Gram negative and/or anaerobic organisms. These antibacterial agents are commonly used in the United States to treat complicated urinary tract infections and intra-abdominal infections. Some of these products labels have the specific indication “complicated urinary tract infections” and “complicated intra-abdominal infections” or state instead that the product is indicated for the treatment of severe or serious systemic infections caused by Gram negative and/or anaerobic organisms, which cause urinary and/or abdominal infections.

Table 1: Antibacterial agents used for treatment of cUTI

Ceftriaxone
Ceftazidime
Cefepime
Ciprofloxacin
Levofloxacin
Aztreonam*
Ampicillin-sulbactam
Ticarcillin-clavulanate
Piperacillin-tazobactam
Imipenem
Doripenem

* Alternative in the setting of beta lactam allergy.

Table 2: Antibacterial agents used for treatment of cIAI (gram-negative and anaerobic pathogens)

Ampicillin-sulbactam[•]
Piperacillin-tazobactam
Ticarcillin-clavulanate
Ceftriaxone[§] or ceftazidime[§]
Moxifloxacin
Ciprofloxacin
Metronidazole
Imipenem-cilastatin
Meropenem
Doripenem
Ertapenem[¥]
Lincosamides (anaerobic coverage)

Clindamycin[§]

• *E. coli* resistance to ampicillin-sulbactam is emerging in some areas. This regimen is NOT recommended for *Pseudomonas* coverage.
§: The product label for these antibacterial agents does not directly address their use in combination with a specific antibacterial agent. However, in clinical practice they are used in combination with another antibacterial agent to cover both Gram negative and anaerobic organisms.
¥ Ertapenem lacks activity against *Acinetobacter* and *Pseudomonas*.

2.3 Availability of Proposed Active Ingredient in the United States

Ceftolozane/tazobactam is not available as a marketed product in the United States or in any other country.

2.4 Important Safety Issues With Consideration to Related Drugs

Ceftolozane is a cephalosporin in the class of beta-lactam antibacterial products, a group of drugs that includes penicillins and cephalosporins. Therefore, it is expected to share some of the safety profile characteristics of other drugs in this class. Penicillins and cephalosporins are associated with IgE-mediated allergic reactions, with varying degrees of severity from mild to life threatening, including rash, pruritus, urticarial, angioedema, anaphylactic shock and other hypersensitivity and immune-mediated reactions in the lungs and kidneys such as pulmonary infiltrate with eosinophilia (PIE) syndrome and glomerulonephritis associated with hypersensitivity angiitis or serum sickness. Renal function impairment has also been associated with cephalosporins, especially when used with aminoglycosides and/or diuretics. Cephalosporins may cause liver dysfunction and cholestasis and, in some cases, hypersensitivity hepatitis. A cephalosporin, ceftriaxone, has been associated with biliary sludge and pseudocholelithiasis, particularly in children. The penicillins are the most common antibacterial agents to cause encephalopathy and high doses of beta-lactams can cause seizures. Beta-lactams may cause several types of immune-mediated reactions, such as hemolytic anemia, characterized by a positive non-gamma Coombs test or by subacute extravascular hemolysis with a positive gamma Coombs test. This latter reaction generally requires prolonged, high-dose therapy and signs of hypersensitivity are usually absent. Acute immune thrombocytopenia has been associated with beta-lactam administration.
Diarrhea is a frequent nonspecific complication of antibacterial therapy. All antibacterial drugs can predispose to *Clostridium difficile* pseudomembranous colitis, and cephalosporins and beta lactams are commonly implicated. Some cases may be life threatening.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- An End of Phase 2 meeting was held on November 4, 2010. The design of Phase 3 trials for cUTI and cIAI was discussed.
- Amended protocols for both indications were submitted on January 24, 2011. Agreements about non-inferiority margin and inclusion of discrete intra-abdominal abscesses and allowance

of enrollment of pre and postoperative enrollment with 24 hours of antibacterial therapy were reached on October 14, 2011.

- The two Phase 3 trials for treatment of cUTI (CXA-cUTI-10-04, CXA-cUTI-10-05) started enrollment in the third quarter of 2011.
- The two Phase 3 trials for treatment of cIAI (CXA-cIAI-10-08 and CXA-cIAI-10-09) started enrollment in the third quarter of 2011 and the first quarter of 2012, respectively. The database lock date for all Phase 3 trials was October 15, 2013.
- On August 29, 2012, Cubist submitted a position paper to the Agency and requested feedback on the classification of beta-lactam antibiotics and the implications for manufacturing their product ceftolozane/tazobactam. The Division initiated the review along with several internal consultations.
- The Division reviewed the proposal with several internal consultations, confirmed the classification of tazobactam as a sensitizing agent and requested a fully dedicated line for manufacturing tazobactam on January 15, 2013.
- On November 21, 2012, and based on our Guidance for Industry for cIAI, published in September 2012, Cubist obtained our agreement to proceed with a single-study strategy for the cUTI and cIAI indications achieved by pooling data from the 2 identical Phase 3 cUTI protocols and the 2 identical Phase 3 cIAI protocols, providing one database per indication with appropriate total sample size and adequate power. The data from the individual protocols for each indication were pooled after database lock, analyzed as 1 dataset, and reported in 1 clinical study report per indication.
- The sponsor's Qualified Infectious Disease Product (QIDP) designation requests for ceftolozane/tazobactam for the indications of cIAI and cUTI were granted on December 5, 2012, and February 20, 2013, respectively.
- Fast Track designation requests for cIAI and cUTI were granted on February 20, 2013, and May 7, 2013, respectively.
- On June 21, 2013 the Division provided comments on the statistical analysis plan describing the pooling of the studies. For the cIAI indication, the Division agreed to the proposed sample size of 988 patients to ensure approximately 90% power to demonstrate the non-inferiority of ceftolozane/tazobactam and metronidazole vs. meropenem in adult subjects with cIAI based on the 95% confidence interval (CI) around the difference in the clinical cure rates at the TOC visit in the microbiological intent-to-treat (MITT) population, using a 10% non-inferiority margin.
- For the cUTI indication, the Division agreed on a combined new sample size of 954 as a single trial to ensure 90% power to demonstrate the non- inferiority of ceftolozane/tazobactam to levofloxacin at a 10% non-inferiority margin.
- On September 24, 2013, the initial Pediatric Study Plan was agreed upon. Three nonclinical studies have been completed. Three safety and pharmacokinetics clinical studies from birth to <18 years of age in cUTI and cIAI indications are planned..
- On December 6, 2013, the sponsor submitted a request for a Request for Submissions of Portions of an Application and a Type-B, pre-NDA meeting, submitted to IND 104,490.
- On January 14, 2014, a Type A meeting was held where Cubist confirmed that the final product would be a co-filled, single vial, manufactured in a fully dedicated line.

- Rolling Review was granted January 31, 2014.
- On February 10, 2014, a pre-NDA meeting was held. The Division agreed to timelines as follows:
    - Additional stability data (9 months) on three registration batches would be submitted as a minor component amendment to the NDA within 60 days of Electronic Submission Gateway (ESG) receipt date.
    - An amendment for submission of the remaining sterility assurance validation package and notification of readiness for the pre-approval inspection of the manufacturing facility, SteriPharma, no later than August 25, 2014.
    - Cubist would submit the last unit of the NDA, containing clinical datasets by late April (it was received on April 21st, 2014).
    - Cubist would include relevant sections of the prescribing information (e.g., nonclinical toxicology) specific to tazobactam from the approved Zosyn® package insert in the draft ceftolozane/tazobactam package insert.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized in electronic Common Technical Document (eCTD) format as described in the CDER guidance entitled *Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications;* June 2008.
A Reviewer's Guide located in the module 5 folder was of good quality and utility. There were no missing datasets and overall the quantity and quality of the submission was adequate to start the review. There were no invalid MedDRA coding in the clinical datasets submitted. The clinical summaries and narratives were comprehensive. Some issues were identified in the complicated intra-abdominal indication review, which made it necessary to ask the sponsor for additional detailed information about prior and concomitant use of antibacterial agents, such as type and duration of treatment, number of procedures performed after 72 hours of the first one to control the infection, and listings of patients with an outcome of cure who required additional surgical procedures to control the infection. In addition, sample informed consent forms were requested from the Applicant.

3.2 Compliance with Good Clinical Practices

All studies were conducted in accordance with International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) consolidated guidelines and the ethical principles of the Declaration of Helsinki. The sponsor has submitted a statement of compliance for the two pivotal studies supporting the cUTI and cIAI indications. Each site signed either the Statement of Investigator Form (Food and

Drug Administration [FDA 1572]) or the Non-United States (US) Investigator Form (CL-FRM-035). Documentation of laboratory quality assurance certificates were provided in the submission.

Complicated Intra-abdominal infections study

This study was initiated between December 8, 2011 (CXA-cIAI-10-08 study) and April 11, 2012 (CXA-cIAI-10-09) and September 10, 2013 (last patient completed study CXA-cIAI-10-08) and October 10, 2013 (last patient completed study CXA-cIAI-10-09) at 196 study centers (102 sites versus 94 sites in the CXA-cIAI-10-08 and CXA-cIAI-10-09 studies, respectively); 128 sites (67 sites versus 61 sites in the CXA-cIAI-10-08 and CXA-cIAI-10-09 studies, respectively) enrolled at least 1 subject. Audit certificates were provided for 23 study sites. The ICF was translated into the local subjects' language: Afrikaans, Arabic, Bulgarian, Croatian, Czech, Dutch, Estonian, French, Georgian, German, Gujarati, Hebrew, Hindi, Hungarian, Kannada, Korean, Latvian, Lithuanian, Malayalam, Marathi, Moldovan, Polish, Portuguese, Romanian, Russian, Serbian, Slovak, Sotho, Spanish (Latin America), Spanish (Spain), Ukrainian, Urdu, Xhosa and Zulu.

Complicated Urinary Tract Infections study

This study was conducted between July 28, 2011 and May 29, 2013 at 209 study centers worldwide. The submission includes a statement that the study was conducted in compliance with IRB and ICH GCP guidelines. Audit certificates for 25 study sites were submitted. The protocol and informed consent form were approved by independent IRBs. A list of the IRBs was provided.
All subjects signed an informed consent that was translated to the subject's language (Estonian, Russian, Latvian, Lithuanian, Portuguese, Spanish, Georgian, German, Hungarian, Hebrew, Arabic, Romanian, Serbian, Slovakian, Afrikaans, Zulu, and Thai).

Site inspections

Six sites were selected for inspection by the Office of Scientific Investigations (OSI, CDER) and DAIP. Since government travel to Russia and Ukraine was not permitted during the time of this review, the selection focused on Eastern European and Latin American sites with high enrollment and/or high treatment effect favoring the active study drug arm (ceftolozane/tazobactam). OSI also inspected the sponsor (Cubist) because ceftolozane/tazobactam is a new molecular entity (NME). Preliminary findings up to the date of this review are presented below. These were provided by Dr. Sharon Gershon, OSI.

Table 3: Preliminary Results of GCP Inspections for NDA 206829

Name of CI/Address	Protocol # and # of Subjects	Inspection Dates	Final Classification
Gintaras Cesnauskas Hipodromo str. 13 Kaunas, LT-45130 LTU Eastern Europe	**Site 6380** CXA-cIAI-10-09 27 subjects	September 8 – 12, 2014	Preliminary VAI
Michal Nowicki Oddzial Kliniczny Nefrologii, Hipertensjologii i Transplantologii Nerek, ulica Kopcinskiego 22 Lódz, LÓDZKIE 90-153 POL Eastern Europe	**Site 5801** CXA-cUTI-10-05 19 subjects	September 1 – 5, 2014	Preliminary VAI
Anca-Ileana Ruxanda Strada Tabaci Numar 1 Craiova, DOLJ 200642 ROU Eastern Europe	**Site 4720** CXA-cIAI-10-08 30 subjects	September 1 – 9, 2014	Preliminary NAI
Gregorio Sanchez Vallejo Cra 14 Cl 17N, Avenida Bolivar Hospital Juan de Dios Pisa Sexto Oficina de Medicina Interna Armenia, Colombia Latin America	**Site 7404** CXA-cUTI-10-04 27 subjects	September 8 – 12, 2014	Preliminary VAI
Andres Tein L. Puusepa 8 Tartu, 51014 EST Eastern Europe	**Site 6275** CXA-cIAI-10-09 40 subjects	September 11 – 17, 2014	Inspection ongoing
Egils Vjaters Pilsonu str. 13 Riga, LV-1002 Latvia, Eastern Europe	**Site 6602** CXA-cUTI-10-04 28 subjects	September 22-26, 2014	Inspection pending
Cubist Pharmaceuticals, Inc. 65 Hayden Avenue Lexington, MA 02421	Sponsor Inspection:	August 19 – September 4, 2014	Preliminary NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

Six foreign clinical investigator inspections (three sites for the cIAI protocol and three sites for the cUTI protocol) and a sponsor site inspection (Cubist Pharmaceuticals) were conducted in support of NDA 206829. All classifications shown in the last column above are preliminary, as no EIRs have been received or reviewed to date. No regulatory violations were found during the inspection of the Sponsor. The inspection of Site 6275 (Tein, Estonia) is ongoing this week. The inspection at Site 6602 (Dr. Vjaters, Latvia) is pending. At **Site 6380** (Cesnauskas) minor regulatory violations were found and a FDA 483 was issued for the failure to maintain accurate records: contemporaneously document the infusion times, to have documented training records for the study nurses performing the infusions and for mis-randomizing approximately 5 of 28 subjects enrolled. At **Site 5801** (Nowicki, Poland) an observational FDA 483 was issued for not following the investigational plan: alkaline phosphatase testing not being performed which was needed for inclusion exclusion criteria; not all subjects with pyelonephritis had blood cultures taken, and some subjects who did not meet urine culture micro criteria were not discontinued. At **Site 7404** (Vallejo, Latin America) a one observation FDA 483 was issued for inaccurate records – 9 of 13 subjects reviewed did not have concomitant medications documented.

3.3 Financial Disclosures

The Applicant submitted form 3454 certification of financial interest in accordance with 21 CFR part 54 for each of the phase 3 clinical studies. The applicant identified a participating sub-investigator in Study CXA-cIAI-10-08, (b) (6) from site number (b) (6) with financial interest. Please see the Financial Disclosure Form in Appendix 1.

(b) (6) reported a financial interest to Cubist via Financial Disclosure Forms stating that the nature of the interest was "ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria (>$25,000 cumulatively)." The site was contacted by the Applicant for further details, and it was reported by the site that (b) (6) was paid by Cubist for speaking engagements.

(b) (6)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

According to the CMC reviewer, Dr. Suresh Pagay, the submission has provided sufficient information to assure the identity, strength, purity, and quality of the drug product, with approval dependent on

satisfactory resolution of all CMC related issues. Stability data at 9 months and 12 months are under review for consideration of shelf life for 12 months. Manufacturing sites inspections by the CDER Office of Compliance are scheduled and approval will be contingent on the inspection findings.

The proposed commercial finished product is sterile powders of ceftolozane drug product intermediate (DPI) and tazobactam sodium (b) (4) filled into single vials, and the drug product formulation is the same as that used in the pivotal Phase 3 trials. The drug product Ceftolozane/Tazobactam for Injection, 1000 mg/500 mg, is presented as a combination of two sterile active powders in a single vial intended for reconstitution and intravenous infusion. Each vial of the drug product contains approximately (b) (4) ceftolozane sterile Drug Product Intermediate (DPI) powder that contains 1147 mg ceftolozane sulfate, which is equivalent to 1000 mg ceftolozane free base, as well as approximately 537 mg tazobactam sodium, equivalent to 500 mg tazobactam free acid. At the time of administration, the contents of the vial are reconstituted using 10 mL sterile Water for Injection or 0.9% Sodium Chloride Injection USP followed by further dilution in an infusion bag of 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP, for administration.

The primary container-closure system is a Type I 20 mL molded glass vial with 20 mm neck finish. The vial is enclosed by a 20 mm rubber stopper and 20 mm plastic flip-cap seal with (b) (4).

Unopened vials should be stored at 2 to 8°C (36 to 46°F), protected from light. Reconstituted ceftolozane/tazobactam must be used within (b) (4) For more details please refer to the CMC review by Suresh Pagay, Ph.D.

4.2 Clinical Microbiology

Clinical microbiological results from pivotal safety and efficacy studies are presented in Section 6. In this section, a summary of microbiological activity from preclinical studies is presented. For more information, please refer to the review by Kerian Grande Roche, Ph.D., the microbiology reviewer.

In vitro activity

Activity against aerobic Gram-negative bacteria

The applicant presented results from five surveillance studies of isolates from Europe and North America. Ceftolozane/tazobactam showed activity against *Escherichia coli* strains having an MIC value less than or equal to 8 µg/mL. There were no significant differences between isolates from Europe and North America.

The $MIC_{50/90}$ for *E. coli* is 0.25/0.5 µg/mL, and for strains with an ESBL phenotype the $MIC_{50/90}$ is 0.5/4 µg/mL. No differences in $MIC_{50/90}$ were detected between 2011 and 2012 Europe and U.S. surveillance for this organism. For multi-drug resistant (MDR) *E. coli* isolates, the ceftolozane $MIC_{50/90}$ is 0.5/4 µg/mL, while the ceftazidime $MIC_{50/90}$ is 16/>32 µg/mL.

Ceftolozane/tazobactam has similar activity against isolates of *Citrobacter koseri*, *Morganella morganii*, *Pantoea agglomerans*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, *Salmonella spp.*, *Serratia liquefacians* and *Serratia marcescens*. The MIC_{90} for all of these species is ≤1 µg/mL.

The activity of ceftolozane/tazobactam was also tested against species of *Klebsiella* and *Enterobacter*. As with other cephalosporins, the ceftolozane/tazobactam MIC_{90} values are somewhat higher against these two genera than with other members of the Enterobacteriaceae. The ceftolozane/tazobactam $MIC_{50/90}$ for wild-type *K. pneumoniae* is 0.25/16 μg/mL and for isolates with an ESBL phenotype, the MIC_{90} is >32μg/mL. For *Enterobacter aerogenes*, the ceftolozane/tazobactam $MIC_{50/90}$ is 0.25/4 μg/mL while for *E. cloacae*, it is 0.25/8 μg/mL. One exception to this trend was *Klebsiella oxytoca*, an organism that has a naturally occurring ESBL encoded in its chromosome. The ceftolozane/tazobactam $MIC_{50/90}$ for this organism is 0.25/1 μg/mL.
Ceftolozane/tazobactam showed activity against *P. aeruginosa* ($MIC_{50/90}$ 0.5/4 μg/mL). The applicant states that in combined US and EU 2011 and 2012 surveillance of MDR *P. aeruginosa* isolates, the ceftolozane/tazobactam MIC_{50} is 4 μg/mL, and that it is the lowest of all agents tested.

The activity of ceftolozane has been tested against resistant organisms. These studies utilized genetically engineered or molecularly characterized isolates with diverse β-lactamases. The addition of tazobactam potentiates the in vitro activity of ceftolozane against the majority of Enterobacteriaceae including isolates with AmpC overexpression or common ESBLs such as TEM, CTX-M and SHV. The $MIC_{50/90}$ for *E. coli* strains harboring CTX-M-14 and CTX-M-15 is <0.25/1 μg/mL and 0.5/2 μg/mL, respectively, while for *K. pneumoniae* harboring CTX-M-15, the $MIC_{50/90}$ is 1/64 μg/mL. Ceftolozane/tazobactam is not active against KPC-2 harboring *K. pneumoniae* for which the $MIC_{50/90}$ is >16μg/mL. Ceftolozane/tazobactam has no activity (MIC range 16->32 μg/mL) against strains expressing metallo-β-lactamases including IMP, VIM, SPM and β-lactamases such as VEB, PER and GES. Ceftolozane/tazobactam has potent activity against wild type and β-lactamase positive *Haemophilus influenzae*. The $MIC_{50/90}$ for both is 0.12/0.25 μg/mL.

Activity against Gram-positive and Gram-negative anaerobic bacteria
Ceftolozane has variable activity against anaerobic species. Ceftolozane/tazobactam has activity against the following species based on the $MIC_{50/90}$ values: *Bacteroides fragilis* (1/4 μg/mL), *Clostridium perfringens* (0.25/32 μg/mL), *Fusobacterium* species (≤ 0.125 /0.25 μg/mL) and *Prevotella* species (≤ 0.125 /1 μg/mL). Lesser activity is seen against other species in the *Bacteroides fragilis* group (MIC_{90} values range from 8-32 μg/mL) and activity was limited against both *C. difficile* and other *Clostridium spp*. (MIC_{90} > 256 μg/mL).

Activity against Gram-positive aerobic bacteria
Ceftolozane/tazobactam demonstrated activity against *S. pyogenes* and *S. agalactiae*. The MIC_{90} for both groups is ≤ 0.5 μg/mL. Activity was also demonstrated against viridians streptococci including the *S. anginosus* group (*S. anginosus*, *S. constellatus* and *S. intermedius*) and *S. salivarius*/*vestibularis* group. The $MIC_{50/90}$ for the *S. anginosus* group is 1/4 μg/mL and the *S. salivarius*/*vestibularis* group 0.5/1 μg/mL.
Ceftolozane/tazobactam has limited activity against *Staphylococcus aureus* [MSSA ($MIC_{50/90}$ 16/32 μg/mL) and MRSA ($MIC_{50/90}$ 64/>64 μg/mL)]. It is also inactive against *Enterococcus faecalis* (VSE and VRE) and *Enterococcus faecium* (VSE and VRE) with a MIC_{50} of >64 μg/mL. The $MIC_{50/90}$ for *Staphylococcus epidermidis* (MSSE) is 8/8 μg/mL and for *S. epidermidis* (MRSE) the $MIC_{50/90}$ is 16/32 μg/mL. The in vitro activity of ceftolozane/tazobactam against *Streptococcus pneumoniae* varied according to susceptibility to penicillin. When tested against penicillin-susceptible strains, the MIC

$_{50/90}$ is ≤0.12/0.12 μg/mL; for penicillin-intermediate strains, the MIC $_{50/90}$ is 1/4 μg/mL and for penicillin-resistant strains, MIC $_{50/90}$ is 8/16 μg/mL.

Mechanism of Resistance

Single and multiple in vitro passage studies as well as 10-day hollow-fiber models indicate a low potential for development of resistance in *P. aeruginosa* and ESBL-positive *Escherichia coli.* In *Pseudomonas 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.

Antimicrobial interaction studies

The effect of combining ceftolozane/tazobactam with other antimicrobial agents was assessed using the checkerboard method and determining the fractional inhibitory concentration (FIC) index. Strains of *E. coli* (2 ESBL negative and 2 ESBL positive), *K. pneumoniae* (2 ESBL negative and 2 ESBL positive), and *P. aeruginosa* (2 each ceftazidime-susceptible, ceftazidime- resistant and imipenem-resistant) were exposed to combinations of ceftolozane/tazobactam and meropenem, amikacin, aztreonam, levofloxacin or tigecycline. No instances of antagonism were seen. Synergy was observed with 15 (21%), additivity with 53 (76%), and indifference with 2 (3%). In another study, ceftolozane/tazobactam was tested in combination with 4 antibiotics active mainly against Gram-positive organisms (rifampin, linezolid, daptomycin, and vancomycin), with gentamicin, which is active against both Gram-positive and Gram-negative bacteria, and with colistin, which is active only against Gram-negative bacteria. The organisms tested included ATCC strains of *E. coli*, *P. aeruginosa* and *S. aureus*, as well as an ESBL-positive strain of *E. coli* and an MDR strain of *P. aeruginosa*. Among the 30 checkerboards, 28 (93%) showed indifference and 2 showed synergy. Ceftolozane/tazobactam was also tested in combination with metronidazole against 3 *E. coli* and 2 *K. pneumoniae* strains. Checkerboards were prepared in Mueller Hinton Broth II medium and incubated aerobically, anaerobically and in a microaerophilic environment. In all cases, where an endpoint could be determined, the result was indifference (FIC index >0.5 and ≤4).

4.3 Preclinical Pharmacology/Toxicology

Please see the pharmacology-toxicology review by Dr. James Wild for details. Key safety findings from the preclinical studies are summarized below.

Safety Pharmacology

The applicant conducted GLP toxicity studies with ceftolozane in rats and dogs. Ceftolozane showed no potential to affect the functioning of the cardiovascular, respiratory, and central nervous systems across nonclinical species at clinically relevant blood concentrations. C_{max} values for all safety pharmacology studies conducted with ceftolozane were estimated based upon Day 1 C_{max} values observed in the pivotal GLP toxicity studies conducted in rats and dogs.

Ceftolozane demonstrated no effect on the human ether-à-go-go related gene (hERG) channel up to a maximum concentration of 667 μg/mL. No significant effects upon cardiovascular functioning were seen in male rats or dogs following IV administration of ceftolozane at 100 mg/kg. Bolus IV administration of ceftolozane to rats at 320 mg/kg produced a slight but statistically significant decrease in heart rate (11%) as compared to pre-dose values.

A statistically significant decrease in heart rate (22%) and mean blood pressure (27%) as compared to predose values was observed at 1000 mg/kg. Following IV administration to dogs, ceftolozane produced a transient 37% increase in heart rate in one animal in the 300 mg/kg dose group with no effects upon ECGs.

Ceftolozane did not produce respiratory or neuropharmacological effects in rats up to a maximum dose 689 mg/kg. The potential for ceftolozane to induce convulsions following ICV injection to mice and rats was 24-and 7.4-fold less, respectively, as compared to the cephalosporin cefoselis. Ceftolozane solutions less than 3000 μg/mL did not induce histamine release from human white cells in vitro.

General and Special Toxicities

Ceftolozane
Ceftolozane in 28-day studies in both rats and dogs with doses as high as 1000 mg/kg/day, produced dose-dependent renal changes in the form of hyaline droplet formation in proximal tubules of the renal cortex. This form of kidney pathology, which is observed with other cephalosporin antibiotics, is thought to represent an adaptation allowing compound disposition via lysosomes. Hyaline droplet formation was a consistent but reversible effect. In the absence of toxicologically meaningful degeneration or necrosis of renal tubular epithelium or substantial changes in relevant clinical pathology parameters including serum BUN, creatinine, inorganic phosphorus and/or urine volume, the hyaline-droplet formation was not considered adverse. No significant platelets or coagulation (aPPT, PT and fibrinogen) toxicities were observed with ceftolozane alone in a 28-day study in rats (Study No. CXA201-T-001). In another 28-day rat study, 6.4% to 7.8% reductions in aPTT was observed in females only. The no observed adverse effect level (NOAEL) identified in the pivotal 4-week Good Laboratory Practice (GLP) studies is considered to be 1000 and 300 mg/kg/day for rats and dogs, respectively. The NOAEL of 300 mg/kg/day for dogs was based on the presence of the cephalosporin-induced, histamine-related adverse clinical signs at 1000 mg/kg/day (namely, flush of the auricular and oral mucosa, swelling of the head, emesis, salivation, as well as lateral position and not kidney-related effects).
Ceftolozane safety margins for cIAI and cUTI based on general toxicity studies conducted in rats and dogs range from 2.6- to 10.3-fold based on AUC and 13.3- to 141-fold based on Cmax.

Tazobactam
The primary pathology associated with tazobactam administration in the rat and dog 28-day, repeated-dose, IV-combination studies as well as published 6-month repeated-dose studies in rat (intraperitoneal administration at 80 mg/kg/day) and dog (IV administration at 160 mg/kg/day) was a dose-dependent liver histopathology consistent with the accumulation of liver glycogen and increased smooth endoplasmic reticulum. The histopathology occurred diffusely in liver sections, was reversible, and

was characterized by accumulation of pale, eosinophilic, foamy to finely vacuolated, material within the cytoplasm of hepatocytes. In rat studies, dose-dependent serum chemistry changes including decreased triglycerides, albumin, and glucose and increased globulin and potassium were considered to be related to the liver changes and glycogen accumulation. However, because changes were generally of low magnitude, reversible, and not associated with toxicologically meaningful degeneration or necrosis of hepatocytes or biologically meaningful changes in liver enzymes, the changes were not considered adverse. Higher doses of tazobactam were also associated with dose-dependent decreases in hematocrit, hemoglobin, and red blood cell counts, as well as occasional increases in platelets and the percent of lymphocytes. Doses of 500/mg/kg/day for 28 days were associated with a mean platelet increase of 29% in males and 31% in females. A 5.5% to 9% shortening of aPTT was also observed in this study. These toxicities were not reproducible in dogs or in another 4-week rat study at similar doses. However, the hematology changes were generally mild, reversible, and did not extend to bone marrow pathology. The NOAEL determined for both rats and dogs was 40 mg/kg/day. Tazobactam safety margins range from 1.1- to 6.6-fold based on AUC and 10.4- to 15.4-fold based on C_{max}.

Ceftolozane/tazobactam combination studies

In repeated-dose combination studies with administration of ceftolozane plus tazobactam as well as each compound alone in rats (1-month) and dogs (2-weeks), new or augmented toxicities were not observed. As in previous studies using the single agents, dose-dependent reversible hyaline droplet formation in kidneys was observed with the administration of ceftolozane and dose-dependent, reversible glycogen accumulation in liver occurred with tazobactam administration in rats. In the dog combination study, using high-doses of 300/150 mg/kg/day ceftolozane/tazobactam, toxicities were absent. In both rats and dogs, plasma concentrations of ceftolozane and tazobactam were not changed when the compounds were administered in combination and plasma concentrations for both agents did not increase with repeated dosing. In a 28-day rat combination study with ceftolozane/tazobactam in doses of 1000/500 mg/kg/day, mean increases in platelets of 29% to 31% were observed, together with a mean shortening of aPTT. These changes were similar to those observed in the tazobactam alone arm and were not increased by the addition of ceftolozane. Other rat and dog studies do not reproduce these findings.

Other toxicities included cecal enlargement, injection site reactions, histamine release, and, under sensitizing conditions, antigenicity. Cecal enlargement occurred with both ceftolozane and tazobactam administered alone in rats. This effect, commonly associated with antibiotic treatment in rodents and rabbits, was not reported to become more severe with combination treatment.

Injection-site reactions including erythema, edema, desquamation, subcutaneous hemorrhage, perivascular hemorrhage, perivascular fibrosis, inflammation and scabbing occurred for both ceftolozane and tazobactam but only with repeated-dosing in mice and rats. The effects were dose-and concentration-dependent. In addition to an absence of injection-site reactions in dogs, no injection-site reactions were reported for the combination rat study where maximal concentrations of ceftolozane and tazobactam were 200/100 mg/ml, values much greater than the concentrations recommended for clinical administration (10 mg/ml ceftolozane and 5 mg/ml tazobactam).

Ceftolozane did not stimulate histamine release *in vitro* in isolated human peripheral white blood cells, and histamine release and/or histamine-related clinical signs were not noted for rats administered ceftolozane. However, in single- and repeated-dose studies, dogs administered ceftolozane demonstrated increased plasma histamine and clinical signs consistent with histamine release including vomiting, and redness of the ears and oral mucosa. These data suggest dogs are more sensitive than other species to histamine releasing ability of ceftolozane.

Ceftolozane did not stimulate antigenic responses in mice, but guinea pigs actively sensitized to ceftolozane in the presence of Freund's adjuvant experienced systemic anaphylaxis reactions upon re-exposure to ceftolozane alone. The same animals experienced positive antibody titers associated with passive cutaneous antibody reactions. These results suggest that ceftolozane, while not greatly antigenic, has the potential to elicit allergic reactions like other beta-lactam antibiotics.

Carcinogenicity and Genetic Toxicity

Ceftolozane and tazobactam are only recommended for short-term administration (≤ 14 days). Consequently nonclinical carcinogenicity assessments were not recommended for either compound. Also the weight of evidence suggests both ceftolozane and tazobactam and their combination do not pose a strong potential for genotoxicity in humans. The combination of ceftolozane and tazobactam (ZERBAXA) was assessed in several *in vitro* and *in vivo* genetic toxicity assays. ZERBAXA was negative for genotoxicity in an *in vitro* mouse lymphoma assay and an *in vivo* rat bone marrow micronucleus assay. In an *in vitro* Chinese hamster ovary cell chromosomal aberration assay, ZERBAXA was positive for structural aberrations. Similarly, ceftolozane alone was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* Chinese hamster lung fibroblast cell chromosomal aberration assay, an *in vivo* mouse micronucleus assay, and an *in vivo* unscheduled DNA synthesis (UDS) assay. While positive results for mutagenicity were obtained for ceftolozane in an *in vitro* mouse lymphoma assay. Tazobactam alone was negative for genotoxicity in all assays including in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* Chinese hamster lung fibroblast cell chromosomal aberration assay, and an *in vivo* rat bone marrow micronucleus assay.

Reproductive and Developmental Toxicity

In a rat fertility study, ceftolozane had no adverse effects on fertility in males or females at intravenous doses up to 1000 mg/kg/day. The mean plasma exposure (AUC) value at this dose is approximately 8 times the mean daily clinical ceftolozane exposure value. In a rat fertility study with intraperitoneal tazobactam, male and female fertility parameters were not significantly affected at doses ≤ 640 mg/kg/day (approximately 4 times the recommended clinical daily dose based on body surface area comparison).

Embryo-fetal development studies performed in mice and rats with ceftolozane doses up to 2000 and 1000 mg/kg/day, respectively, revealed no teratogenicity and no evidence of harm to the fetus. The mean plasma exposure (AUC) values associated with these doses are approximately 19 (mice) and 11 (rats) times the mean daily human ceftolozane exposure at the clinical dose of 1 gram administered three times per day. It is not known if ceftolozane crosses the placenta in animals. In an embryo-fetal study in rats, tazobactam administered at doses up 3000 mg/kg/day (approximately 19 times the

recommended human dose based on body surface area comparison) did not produce maternal toxicity, fetal toxicity, or teratogenicity. In rats, tazobactam was shown to cross the placenta. Concentrations in the fetus were less than or equal to 10% of those found in maternal plasma.

In a pre- postnatal study in rats, ceftolozane administered during pregnancy and lactation (Gestation Day 6 through Lactation Day 20) was associated with a decrease in auditory startle response in postnatal day 60 male and female pups at maternal doses of ≥ 300 mg/kg/day. The plasma exposure (AUC) associated with the NOAEL dose of 100 mg/kg/day in rats is approximately equal to the mean human ceftolozane exposure at the clinical dose of 3 grams/day. In a pre-postnatal study in rats, tazobactam administered intraperitoneally twice daily at the end of gestation and during lactation (Gestation Day 17 through Lactation Day 21) produced decreased maternal food consumption at the end of gestation and significantly more stillbirths with a tazobactam dose of 1280 mg/kg/day. No effects on the development, function, learning or fertility of F1 pups were noted, but the postnatal body weights for F1 pups from dams receiving 320 and 1280 mg/kg/day tazobactam were significantly reduced 7 and 21 days after delivery respectively. F2 generation pups were normal for all maternal doses of tazobactam. The NOAEL for reduced F1 body weights was considered to be 40 mg/kg/day (approximately 0.3 times the recommended human dose based on body surface area comparison). Exclusive of reduced body F1 body weights, the NOAEL was considered to be 320 mg/kg/day or approximately equal to the recommended human dose based on body surface area comparisons.

4.4 Clinical Pharmacology

The proposed regimen for ceftolozane/tazobactam is 1.5 g every 8 hours by IV infusion administered over 1 hour for patients ≥18 years of age with creatinine clearance (CrCL) >50 mL/min for 7 days in the treatment of complicated urinary tract infections and for 4 to 14 days for the treatment of complicated intra-abdominal infections. For more details about clinical pharmacology (including the FDA recommended dose adjustments for renal impairment) please refer to the review of Ryan Owen, Ph.D., the clinical pharmacology reviewer.

4.4.1 Mechanism of Action

Like other members of the cephalosporin class, ceftolozane exerts its bactericidal activity by inhibiting essential penicillin-binding proteins (PBPs), resulting in inhibition of cell wall synthesis and subsequent cell death. Ceftolozane is a PBP3 inhibitor, and shows affinities for all essential PBPs (1b, 1c, and 3) in *P. aeruginosa.*

Tazobactam is an irreversible inhibitor of chromosomal- and plasmid-mediated bacterial class A and some class C β-lactamases that, by binding to the active site of these enzymes, protects ceftolozane from hydrolysis, broadening its spectrum to include most ESBL-producing *E. coli*, *K. pneumoniae*, and other Enterobacteriaceae, as well as some anaerobic pathogens (i.e., *B. fragilis*). Tazobactam has no intrinsic antibacterial activity (MIC >16 µg/mL).
The addition of tazobactam has no significant impact on the antipseudomonal activity of ceftolozane, since *P. aeruginosa* rarely produces ESBLs.

4.4.2 Pharmacodynamics

PK/PD parameter of interest
Similar to other cephalosporin-class drugs, the %T>MIC was identified as the PK/PD parameter most closely associated with efficacy in animal models of infection for ceftolozane. The %T > a threshold concentration was identified as the PK/PD parameter most closely associated with efficacy for tazobactam using in vitro infection models.

Cardiac electrophysiology
In a randomized, positive and placebo-controlled crossover thorough QTc study, 51 healthy subjects were administered a single therapeutic dose (1.5 g) and a supra-therapeutic dose (4.5 g) of ceftolozane/tazobactam. No significant effects of ceftolozane/tazobactam on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected. Therefore, ceftolozane/tazobactam does not affect cardiac repolarization.

4.4.3 Pharmacokinetics

General
The pharmacokinetics of ceftolozane and tazobactam are linear. The C_{max} and AUC of both ceftolozane and tazobactam increased in a dose-proportional manner over the dose ranges studied. The elimination half-life of ceftolozane was typically 2-3 hours and the elimination half-life of tazobactam is approximately 1 hour.

Absorption
ZERBAXA is intended for intravenous administration only. Therefore, no studies pertaining to absorption were conducted (e.g., BA/BE, food effect, in vitro dissolution, etc.).

Distribution
The V_{ss} of subjects was independent of dose and exceeded plasma volume for ceftolozane and tazobactam, thus indicating the distribution of ceftolozane and tazobactam to the extracellular space.

The protein binding of ceftolozane in human plasma proteins ranged from 16% to 21%. The protein binding of tazobactam is approximately 30%.

Metabolism
Ceftolozane undergoes little to no metabolism. Tazobactam is partially (~20%) metabolized to tazobactam M-1 via hydrolysis of the β-lactam ring. Tazobactam M-1 lacks pharmacological and antibacterial activity.

Excretion
Ceftolozane, tazobactam, and tazobactam M-1 are all primarily renally eliminated.

Intrinsic factors

No dose adjustment is required in patients with mild renal impairment as the observed increases in exposure were not clinically significant in the renal impairment trials. A dose adjustment of ceftolozane/tazobactam will be required in patients with moderate renal impairment, severe renal impairment, and ESRD. The dose adjustments proposed by the applicant are still under review.

No dose adjustment is recommended on the basis of any other intrinsic factor (e.g., hepatic impairment, geriatric patients, gender, or race).

Extrinsic factors

In vitro studies demonstrated that ceftolozane, tazobactam, and the M-1 metabolite of tazobactam did not inhibit or induce the common CYP450 enzymes at therapeutic plasma concentrations. In vitro induction studies showed that ceftolozane, tazobactam, and tazobactam M-1 metabolite decreased CYP1A2 and CYP2B6 enzyme activity and mRNA levels in primary human hepatocytes as well as CYP3A4 mRNA levels at supratherapeutic plasma concentrations. A clinical drug-drug interaction study was conducted to further investigate these findings, and the review is still pending.

Ceftolozane and tazobactam were not substrates for P-gp or BCRP, and tazobactam was not a substrate for OCT2, *in vitro* at therapeutic concentrations. Tazobactam is a known substrate for OAT1 and OAT3. Co-administration of tazobactam with OAT1/OAT3 inhibitor probenecid has been shown to prolong the half-life of tazobactam by 71%. Co-administration of ZERBAXA with drugs that inhibit OAT1 and/or OAT3 may increase tazobactam plasma concentrations.

In vitro data indicate that ceftolozane did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, MRP, BSEP, OAT1, OAT3, MATE1, or MATE2-K *in vitro* at therapeutic plasma concentrations.

In vitro data indicate that neither tazobactam nor the tazobactam metabolite M1 inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, or BSEP transporters at therapeutic plasma concentrations. *In vitro,* tazobactam inhibited human OAT1 and OAT3 transporters with IC_{50} values of 118 and 147 µg/mL, respectively. A clinical drug-drug interaction study was conducted and results indicated drug interactions involving OAT1/OAT3 inhibition by ZERBAXA are not anticipated.

Dose Justification

Using the mouse neutropenic model, the ceftolozane %T>MIC targets were determined for Enterobacteriaceae (see table below).

Table 4: Percent T>MIC required for activity against Enterobacteriaceae and *Pseudomonas aeruginosa*

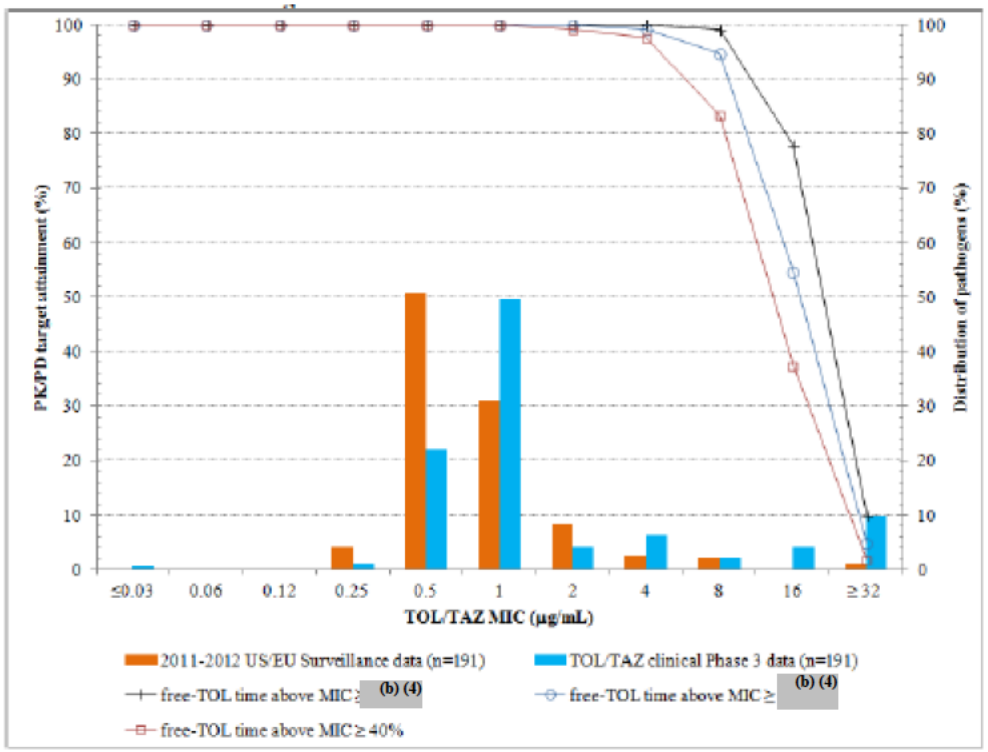
Organism	Ceftolozane MIC (µg/mL)	Percent (%) T > MIC of Ceftolozane		
		Bacteriostasis	1-$\log_{10}$ kill	2-$\log_{10}$ kill
Enterobacteriaceae				
E. coli ATCC 25922	0.5	[redacted] (b) (4)		42.2
E. coli NIH-J	0.06			40.8
K. pneumoniae ATCC 43816	1 – 2			43.4
K. pneumoniae 216	1			40.9
Mean ±SD				**41.8 ± 1.2**
P. aeruginosa				
ATCC 27853	0.5	[redacted] (b) (4)		66.0
4034A	0.5 -1			45.7
PO2	0.5			61.6
313	1			35.5
Mean ±SD				**52.2 ± 14.1**
Overall Median for all strains				**42.8**

%T>MIC=time as a percentage of the dosing interval the drug concentrations exceeds the MIC; ATCC=American Type Culture Collection; MIC=minimum inhibitory concentration; SD=standard deviation

The probability of PK/PD target attainment for 1.5 g ceftolozane/tazobactam are based on median free-drug %T>MIC targets of [redacted] (b) (4) which have been shown to be associated with net bacterial stasis and a 1-$\log_{10}$ colony forming unit reduction from baseline, respectively (see figure below). A 40% T>MIC target is also included for a more conservative estimate (nearly two log kill).

These PTA simulations indicate a >90% chance of achieving 1-$\log_{10}$ kills of *P. aeruginosa* at a dose of 1.5 g ceftolozane/tazobactam. The dose is further supported by successful Phase 2 trials in cIAI and cUTI.

Figure 1: Percentage of Simulated Subjects Achieving Free-Drug %T>MIC Targets and *P. aeruginosa* MIC Distributions



%T>MIC=time as a percentage of the dosing interval that the total drug concentration exceeds the MIC; EU=European Union; MIC=minimum inhibitory concentration; PK/PD=pharmacokinetic/pharmacodynamic; TAZ=tazobactam; TOL=ceftolozane; US=United States
Simulated subjects with Normal Renal Function

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The primary data to support the safety of ceftolozane/tazobactam in subjects with cUTI and cIAI are derived from an integrated analysis of the Phase 3 studies (for cUTI: CXA-cUTI-10-04 and -05 and for cIAI: CXA-cIAI-10-08 and -09). Supportive safety information comes from a total of nine single ascending and multiple dose Phase 1 (2 with ceftolozane and 7 with ceftolozane/tazobactam) and two randomized double-blind Phase 2 studies (one with ceftolozane alone, for cUTI, and one with ceftolozane/tazobactam, for cIAI), as well as data accrued from the single subject enrolled from the discontinued open-label Phase 3 nosocomial pneumonia (NP) study. A total of 305 subjects have been exposed to ceftolozane or ceftolozane/tazobactam in Phase 1 studies, which include a thorough QT study, a drug interactions study and pharmacokinetics and safety measurements in healthy volunteers and patients with renal impairment. In the Phase 2 studies, 85 patients received ceftolozane alone (cUTI study) and 82 received ceftolozane/tazobactam (cIAI study). In the Phase 3 studies, 1275 patients received ceftolozane/tazobactam (for cUTI or cIAI) at the to-be-marketed dose and duration of treatment.

Table 5: Listing of Clinical Studies *(adapted from 5.2 Tabular Listing of all Clinical Studies)*

Study Identifier	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimens; Route of Administration**	**Number of Subjects Receiving Study Drug**	**Study Population**	**Duration of Treatment**
CXA-101-01	Safety, tolerability, PK	Phase 1, single-center, randomized, double- blind, placebo- controlled	TOL <u>Part 1:</u> single ascending doses of 250 mg, 500 mg,1 g, 1.5 g, and 2 g as a 60-minute IV infusion <u>Part 2:</u> multiple ascending doses of 500 mg q8h,1 g q8h, and 1.5 g q12h as a 60-minute IV infusion Saline Placebo as a 60-minute IV infusion	64 (48 test drug;16 placebo) <u>Part 1:</u> 30 test drug; 10 placebo <u>Part 2:</u> 18 test drug; 6 placebo	Healthy volunteers	<u>Part 1:</u> 1 day <u>Part 2:</u> 10 days

CXA-201-01	Safety, tolerability, PK	Phase 1, single center, randomized, double- blind, dose escalation within-cohort crossover (Part 1) and within-cohort parallel (Part 2)	Part 1 (SAD): TOL 500 mg, 1 g, 2 g single dose as 60-minute IV infusions TAZ 250 mg, 500 mg, 1 g single dose as 60-minute IV infusions TOL/TAZ 500 mg/250 mg, 1 g/500 mg, 2 g/1 g single dose as 60-minute IV infusions Part 2 (MAD): TOL 1 g q8h, 2 g q8h, 1.5 g q12h single dose as 60- minute IV infusions TAZ 500 mg q8h, 1 g q8h, 750 mg q12h single dose as 60-minute IV infusions TOL/TAZ 1 g/500 mg q8h, 2 g/1 g q8h, 1.5 g/750 mg q12h single dose as 60- minute IV infusions	58 Part 1: 18 Part 2: 40	Healthy volunteers	Part 1: single dose Part 2: up to 10 days

Table 5: Listing of Clinical Studies (Continued)

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects Receiving Study	Study Population	Duration of Treatment
CXA-ELF-10-03	Safety, tolerability, PK, ELF penetration	Phase 1, open label, multiple-dose, randomized, active-controlled,	TOL/TAZ 3 doses of 1.5 g q8h as a 60-minute IV infusion PIP/TAZ 3 doses of 4000 mg/500 mg q6h as a 30-minute IV infusion	51 (25 test drug, 26 active control)	Healthy volunteers	1 day
CXA-MD-11-07	Safety, tolerability, PK	Phase 1, randomized, double-blind, multidose, placebo- controlled,	TOL/TAZ 3 g q8h as a 60- minute IV infusion TOL/TAZ 1.5 g q8h as a 60- minute IV infusion Saline Placebo as a 60-minute IV infusion	16 (12 test drug, 4 placebo)	Healthy volunteers	10 days
CXA-101-02	Safety, tolerability, PK	Phase 1; open-label, single dose,	TOL 1 g as a 60-minute IV infusion	12	Subjects with normal renal function or mild renal impairment	Single dose
CXA-201-02	Safety, tolerability, PK	Phase 1, open-label, single dose	TOL/TAZ 1.5 g 60-minute IV infusion	24	Subjects with normal renal function, or mild or moderate renal impairment	Single dose

CXA-REN-11-01	Safety, PK	Phase 1, open label, prospective, multicenter	TOL/TAZ Severe renal impairment : 500 mg/250 mg single dose as a 60-minute IV infusion	12	Subjects with severe renal impairment Subjects with ESRD requiring HD	Single dose

Table 5: Listing of Clinical Studies (Continued)

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects Receiving Study	Study Population	Duration of Treatment
CXA-201-02	Safety, tolerability, PK	Phase 1, open-label, single dose	TOL/TAZ 1.5 g 60-minute IV infusion	24	Subjects with normal renal function, or mild or moderate renal impairment	Single dose
CXA-REN-11-01	Safety, PK	Phase 1, open label, prospective, multicenter	TOL/TAZ Severe renal impairment : 500 mg/250 mg single dose as a 60-minute IV infusion ESRD requiring HD: 500 mg/250 mg single dose as a 60-minute IV infusion	12	Subjects with severe renal impairment Subjects with ESRD requiring HD	Single dose

Table 5: Listing of Clinical Studies (Continued)

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects Receiving Study	Study Population	Duration of Treatment
CXA-DDI-12-10	Safety, tolerability, PK,	Phase 1, single center, open label, fixed sequence, cross-over	Period 1 (Day 1): Tablet, 20 mg single oral dose furosemide Period 2 (Day 4): Tablet, 200 mg single oral dose caffeine and Syrup, 2 mg single oral dose midazolam Period 3 (Day 7): TOL/TAZ 1.5 g single dose as a 60-minute IV infusion Period 4 (Day 9): Tablet, 20 mg single oral dose furosemide and single dose TOL/TAZ 1.5 g q8h single dose as a 60-minute IV infusion to Day 15 Period 5 (Days 12 and 15): Tablet, 200 mg single oral dose caffeine and Syrup, 2 mg midazolam	16 .	Healthy volunteers	Single dose Period 1: 1 day Period 2: 1 day Period 3: 1 day Period 4: 3 days Period 5: 4 days

Table 5: Listing of Clinical Studies (Continued)

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects Receiving Study Drug	Study Population	Duration of Treatment
CXA-QT-10-02	Safety, QTc effect, PK	Phase 1, randomized, double- blind, double- dummy, placebo- and active- controlled 4-way crossover	Group A TOL/TAZ 1.5 g single dose as a 60-minute IV infusion and Tablet, placebo Group B TOL/TAZ 3 g/1.5 g single dose as a 60-minute IV infusion and Tablet, placebo Group C Saline Placebo as a Single IV dose and Tablet, placebo Group D Saline Placebo as a Single IV dose Tablet, 400 mg single oral dose moxifloxacin	51 (51 test drug, 51 active control, 50 placebo)	Healthy Volunteers	single dose
CXA-101-03	Safety, efficacy, Population PK analysis	Phase 2, multicenter, prospective, randomized , double-blind	TOL 1 g q8h as a 60-minute IV infusion CAZ 1 g q8h as a 60-minute IV infusion	127 (85 test drug, 42 active control)	cUTI Subjects (including pyelo- nephritis)	7 to 10 days

Table 5: Listing of Clinical Studies (Continued)

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects Receiving Study Drug	Study Population	Duration of Treatment
CXA-IAI-10-01	Safety, efficacy, Population PK analysis	Phase 2, multicenter, prospective, randomized, double- blind, active comparator/ placebo-controlled	TOL/TAZ 1.5 g q8h as a 60- minute IV infusion plus MTZ 500 mg q8h as a 60-minute IV infusion MEM 1 g q8h as a 60- minute IV infusion Saline Placebo as a 60-minute IV infusion	122 (83 test drug; 39 active control)	Subjects with cIAI	4 to 7 days
CXA-cUTI-10-04 10-05	Efficacy and safety	Phase 3, multicenter, randomized. double- blind, active comparator/ placebo-controlled	TOL/TAZ 1.5 g q8h as a 60- minute IV infusion LVX 750 mg q24h as a 60- minute IV infusion Saline Placebo as a 60-minute IV infusion	1068 (533 test drug; 535 active control) (15 randomized, not dosed)	Subjects with cUTI (including pyelo-nephritis)	7 to 9 days

Table 5: Listing of Clinical Studies (Continued)

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimens; Route of Administration	Number of Subjects Receiving Study Drug	Study Population	Duration of Treatment
CXA-cIAI-10-08 10-09	Efficacy, Safety	Phase 3, multicenter, randomized (1:1), double- blind, active comparator/ placebo-controlled	TOL/TAZ 1.5 g q8h as a 60- minute IV infusion plus MTZ 500 mg q8h as a 60-minute IV infusion MEM 1 g q8h as a 60- minute IV infusion Saline Placebo as a 60-minute IV infusion	979 (482 test drug; 497 active control) (15 randomized, not dosed)	Subjects with cIAI	4 to 14 days
Other Study						
CXA-NP-11-08	Efficacy, Safety	Phase 3, multicenter, randomized, open-label	TOL/TAZ 3 g q8h as a 60- minute IV infusion PIP/TAZ 4.5 g q6h as a 30- minute IV infusion	As of the data cut-off (15 October 2013) 1 subject enrolled and randomized to TOL/TAZ	Subjects with VAP	8 days, could be extended to 14 days for subjects with *P. aeruginosa*

a1.5 g TOL/TAZ = 1 g of ceftolozane and 500 mg tazobactam; 3 g TOL/TAZ = 2 g of ceftolozane and 1 g tazobactam.
CAZ = ceftazidime cIAI = complicated intra-abdominal infection; CLCR = creatinine clearance; cUTI = complicated urinary tract infection; CXA-101 = ceftolozane; CXA-201 = ceftolozane/tazobactam; DDI = Drug-drug interaction; ELF = epithelial lining fluid; ESRD = end stage renal disease; HD = hemodialysis; IV = intravenous;
LVX = levofloxacin; MAD = multiple ascending dose; MEM= meropenem; MXF = moxifloxacin; MTZ = metronidazole; PK = pharmacokinetics; PIP = piperacillin; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours; QTc = QT interval; SAD = single ascending dose; TAZ = tazobactam; TOL = ceftolozane; VAP = ventilator-associated pneumonia.

5.2 Review Strategy

The clinical study reports of two small Phase 2 studies (one in the cUTI indication and one in the cIAI indication) were submitted in support of the pivotal Phase 3 studies. These will be discussed briefly in section 5.3. The results of two Phase 3 clinical trials were submitted in support of the cUTI and cIAI indications. These will be discussed in 5.3, along with the two Phase 2 studies, one per indication. A detailed discussion on efficacy findings is presented in section 6.0. Due to some differences in study design, and the small sample size, the Phase 2 and Phase 3 studies were not pooled for analysis. Phase 2 studies were reviewed individually.
Each Phase 3 trial originated from two identical individual Phase 3 trials in each indication, which were pooled after the database lock and before unblinding, at the same time. The overall safety for cUTI and cIAI indications and the efficacy review for the cIAI indication were performed by Maria Allende, M.D., the primary clinical reviewer. The review of clinical efficacy and safety in the cUTI indication was performed by Hala Shamsuddin, M.D. Statistical analyses for efficacy were performed by Daniel Rubin, Ph.D., for the cUTI indication, and Christopher Kadoorie, Ph.D., for the cIAI indication.

5.3 Discussion of Individual Studies/Clinical Trials

This section will provide an overview of the design and rationale of the individual trials that support safety and efficacy for cIAI and cUTI. An overview of protocol amendments and rationale for the individual trials is also provided here. Additional information about the design of the Phase 3 trials for both indications will be discussed in Section 6, under the Methods sections (6.1.1 and 6.2.1), in the context of efficacy findings.
.

Pooling of data

Originally, as part of the development program for ceftolozane/tazobactam for cUTI and cIAI, Cubist initiated two identical prospective, randomized, double blinded and multinational 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 protocol shared the same eligibility criteria, dose and treatment duration, same endpoints and non-inferiority margin, and same schedule of procedures and evaluations. The four studies were conducted between July 2011 and October 2013, in North and South America, Eastern and Western Europe, Australasia, and South Africa, although more than half of the enrollment contributions came from Russia and Eastern Europe.
Enrollment in these four protocols started between December, 2011, and April, 2012. In September, 2012, the new draft Guidance for Industry for complicated intra-abdominal Infections allowed for the possibility of a single study per indication for sponsors developing a drug for more than one indication for treatment of infections caused by similar bacterial pathogens. After discussions with FDA, the applicant submitted a revised protocol and statistical

analysis plan to pool the two Phase 3 studies into one, and finalized enrollment in both trials with a reduced number of patients, with revised sample size and power calculations done over the pooled sample size. The pooling of the patients for each indication from all sites was considered appropriate since both trials within each indication had identical inclusion and exclusion criteria, identical primary efficacy variables, trial drug dosing regimen, comparator, treatment duration, and outcome and safety assessments. Both protocols within each indication were also being conducted in the same regions (with different countries) with expected similar regional representation in each protocol. As part of the agreement, the applicant performed several additional analyses to assess comparability of both studies per indication: the key efficacy parameters, as well as the demographics, baseline characteristics, and prognostics factors, were summarized and numerically assessed side-by-side by protocol number. The internal consistency of the treatment effect was also evaluated.

Cubist obtained agreement from the FDA in November, 2012, to proceed with a single-study strategy for the cUTI and cIAI indications achieved by pooling data from the 2 identical Phase 3 cUTI protocols and the 2 identical Phase 3 cIAI protocols, providing one database per indication and one study report per indication. The pooling of data occurred after database lock, on October 15, 2013, and all studies were unblinded at the same time. A total of 2076 subjects were randomized in the Phase 3 studies and 2047 received study drug at the to-be-marketed dose of 1.5 g of ceftolozane/tazobactam every 8 hours. The table below shows the timelines of the two phase 3 trials to support the cUTI and the cIAI indications

Table 6: Phase 3 cUTI and cIAI study timelines

Study	First Patient Enrolled	Last Patient Completed	Final pooled sample size (N)	Database Lock	CSR completed
CXA-cUTI-10-04	28 July 2011	04 September 2013	1083	September 2013	21 February 2014
CXA-cUTI-10-05	15 September 2011	29 May 2013			
CXA-cIAI-10-08	08 December 2011	10 September 2013	993	October 15, 2013	18 March 2014
CXA-cIAI-10-09	12 April 2012	15 October, 2013			

Complicated Intra-Abdominal Infections

Between December 2011 and April 2012, the Applicant initiated two identical Phase 3 trials, CXA-cIAI-10-08 and CXA-cIAI-10-09, to support the cIAI indication. While enrollment was ongoing, agreement was obtained to finalize both studies with a reduced sample size in order to pool the data after database lock (please see "Pooling of Data" above) into one single study. The total planned pooled sample size was 988 (494 per study). The final pooled database contained a total of 983 patients.

Each Phase 3 study was a multicenter, randomized, double-blind, active-controlled study. A total of 196 sites in 29 countries enrolled patients. Both protocols were conducted in the same regions, including mainly Eastern Europe and South America, and to a lesser extent, Western Europe, North America. Israel, South Korea, India, South Africa and Australia also contributed to a small percentage of enrollments. The countries differed, except for the United States and Latvia, which were common for both studies. The highest enrollers in both protocols were sites in Russia, Eastern Europe and South America, contributing to more than two thirds of the total patient population. The total number of patients enrolled in North America and included in the microbiological intent to treat population was 51 (6.3% of the study population). The original protocol was amended twice, on July 11 and October 5, 2011 (versions 2.0 and 2.1, respectively) to change the treatment duration from 2 to 7 days to **2 to 10** days and the TOC and LFU visit windows (TOC ~~18~~ **26**- to ~~22~~ **30** days, LFU ~~28~~ **38**- to ~~35~~**45** days after the first treatment dose), respectively, and according to FDA guidance. An amendment (version 3.0) followed to increase the sample size to increase statistical power, and the last amendment (for the United States only) was on February 7, 2013, version 3.1, to include the pooling strategy and analysis to support the NDA and to decrease the non-inferiority margin from 12.5% to 10%, all in accordance to FDA recommendations provided in written comments.

Adult patients with cIAI requiring surgical intervention to treat an infection were randomly assigned in a 1:1 ratio to receive ceftolozane/tazobactam (1.5 g every 8 hours) plus metronidazole (500 mg every 8 hours) or meropenem (1 g every 8 hours) with placebo (every 8 hours) for 4 to 10 days. For patients with moderate renal impairment (creatinine clearance 30-50 mL/min) a dose reduction of 50% was made by the unblinded pharmacist. Patients who developed renal failure (creatinine clearance <30 mL/min) were withdrawn from study drug administration. Hospitalization was mandatory during administration of at least the first 9 doses (approximately 3 days) of IV study therapy.

Subjects were stratified at randomization by primary site of infection (bowel versus other site of IAI) and investigational site. The dose of ceftolozane/tazobactam (1.5 g every 8 hours) in the Phase 3 cIAI trials was selected based on a pharmacokinetic/pharmacodynamic (PK/PD) analysis. Human pharmacokinetics data from a total of 198 healthy volunteers and limited pharmacokinetic data from 77 patients from the Phase 2 study in subjects with cIAI provided justification for the dose selected. Metronidazole, an antibacterial agent approved for the treatment of anaerobic infections, and recommended by clinical guidelines in the treatment of cIAI in combination with a cephalosporin, was administered at a dose of 500 mg IV every 8 hours. The schedule of evaluations and procedures, patient population, treatment duration, efficacy endpoints and statistical methods used for analysis were identical for both trials. Once randomized, patients were evaluated for baseline characteristics that included a medical history, physical examination, and laboratory evaluation 24 hours prior to study drug administration. Subsequent assessment for response, safety, laboratory, and other evaluations were scheduled at specific time points (e.g. during study drug treatment, end-of-therapy [EOT], 24 hours after last dose of study drug, test-of-cure [TOC], 26 to 30 days after first dose of study drug, and late follow-up [LFU] visits, 38 to 45 days after first dose of study drug). Baseline assessments included examination of the abdomen and the surgical wound, clinical laboratory tests, physical examination, and vital signs. Clinical response was assessed at the EOT, TOC, and LFU visits and included examination of abdominal signs and symptoms and the surgical wound, clinical laboratory tests, and vital signs.

The primary efficacy endpoint was the clinical response in the microbiological intent-to-treat population assessed by an Investigator at the TOC visit 26 to 30 days after the initiation of study drug. The key secondary efficacy endpoint was the clinical response in the microbiologically evaluable population assessed by an Investigator at the TOC visit 26 to 30 days after the initiation of study drug.

The primary and key secondary efficacy hypotheses of this study were to establish non-inferiority of ceftolozane/tazobactam plus metronidazole versus meropenem with respect to the proportion of subjects who achieved clinical cure at the TOC visit in the microbiological intent to treat (MITT) and microbiologically evaluable (ME) populations, respectively.

The MITT population was defined as all randomized subjects with cIAI with at least 1 baseline intra-abdominal pathogen, regardless of susceptibility to study drug.

Subjects who were clinically cured at the TOC visit were reassessed at the LFU visit (38 to 45 days after the initiation of study drug) for evidence of sustained clinical cure or relapse of symptoms. The planned sample size of 988 subjects (494 per arm) ensured at least 90% power to demonstrate the noninferiority of ceftolozane/tazobactam plus metronidazole to meropenem at a 10% non-inferiority margin and 1-sided significance level of 0.025 in the microbiological intent to treat population. These calculations assumed 80% of randomized subjects would meet the criteria to be included in the MITT population and that the clinical cure rate in both treatment arms would be 75%. A total of 993 subjects were enrolled and randomized, 487 subjects to the ceftolozane/tazobactam plus metronidazole treatment arm and 506 subjects to the meropenem treatment arm of the Intent-to-Treat (ITT) population. The Safety population included 482 subjects in the ceftolozane/tazobactam plus metronidazole and 497 subjects in the meropenem treatment arm that received any amount of study drug.

Approximately 80% of subjects randomized had at least 1 qualifying baseline pathogen such that the MITT population included 389 subjects in the ceftolozane/tazobactam plus metronidazole arm and 417 subjects in the meropenem arm for the primary efficacy analysis.
All subjects in the microbiological intent to treat population with an outcome of failure or those with an outcome of cure who had a second unplanned intra-abdominal intervention were reviewed by an expert, independent Surgical Review Panel (SRP) comprising 3 surgeons, 2 interventional radiologists, and a chairperson to determine the adequacy of the intervention in achieving infection source control. All panel members were blinded to study therapy received and subject identifiers; none of the panel members were involved in the conduct of the study. Subjects who were deemed to have an inadequate source control were excluded from the CE/ME analysis. In addition, subjects with adequate source control at baseline who had an outcome of cure per investigator but had evidence of an ongoing infection at the time of the second procedure, as determined by the SRP, were considered treatment failure in the CE/ME analysis populations. The panel review impacted the clinically evaluable (CE) and microbiologically evaluable (ME) populations only.

Phase 2 Study in cIAI

Prior to initiation of the pivotal Phase 3 study, a single Phase 2 study was conducted to support the development of ceftolozane/tazobactam (CXIA 101/tazobactam) in cIAI.
This phase 2 study, CXA-IAI-10-01, was designed to determine the efficacy, safety, and pharmacokinetic (PK) profile of ceftolozane/tazobactam (1.5 g every 8 hours) plus metronidazole (500 mg every 8 hours) administered as an IV infusion compared with meropenem (1 g every 8 hours) and a matching saline placebo (every 8 hours) administered as an IV infusion in adult subjects with cIAI for 4 to 7 days. The Phase 2 and Phase 3 studies included similar patient populations as reflected in the range of infections eligible for participation, inclusion/exclusion criteria, doses of ceftolozane/tazobactam plus metronidazole as well as comparator, and definitions of clinical response. However, the two studies differed in treatment duration (4 to 7 days in Phase 2 and 4 to 10 days in Phase 3), the timing of the assessment for the primary and secondary endpoints (7 to 14 days after the end of therapy in Phase 2 and 26 to 30 days from the start of therapy in Phase 3), and stratification (localized appendicitis versus other

and bowel versus other, respectively, as important stratification groups based on primary site of infection). Given these important differences, and considering the small sample size of the Phase 2 study, results from this study are presented separately and only as supportive data for the pivotal Phase 3 study.

The Phase 2 study was conducted in 122 patients who were randomized in a 2:1 ratio to treatment with ceftolozane/tazobactam or meropenem, respectively, and were stratified at the time of randomization by the primary site of infection (localized complicated appendicitis versus other site of IAI). Subjects with generalized peritonitis, regardless of the origin (including the appendix), were stratified to the "other site" group during the randomization process. The most common diagnosis in both treatment groups was appendiceal perforation or periappendiceal abscess reported in 49% or more of subjects in both treatment groups. Localized complicated appendicitis was reported in 41.9% of the microbiological intent to treat population. Diffuse peritonitis was reported in 24.4% and 22.1% of the microbiological intent to treat and microbiologically evaluable populations, respectively. Over half of the subjects in both treatment groups had an intraabdominal abscess, most commonly a single abscess. None of the patients had bacteremia at study entry. The incidence and distribution of intraabdominal pathogens isolated at baseline was similar between the treatment groups. As expected, *Escherichia coli* was the most common pathogen, reported in 67.2% and 76.0% of subjects in the ceftolozane/tazobactam and meropenem groups, respectively, in the mMITT population, and in 71.7% and 79.2%, respectively, in the ME population. *Klebsiella pneumoniae* (n = 9, all in the CXA-101/tazobactam group) and *Pseudomonas aeruginosa* (n=7, 4 in the ceftolozane/tazobactam group and 3 in the meropenem group) were the other common baseline Gram- negative aerobes in the microbiological intent to treat population. Gram-positive aerobes, primarily streptococcal and enterococcal species, were isolated in approximately one-third of subjects in both treatment groups. Gram-negative anaerobes, primarily *Bacteroides* species, were isolated in approximately 20% of subjects in both treatment groups, and Gram-positive anaerobes were isolated in <5% of subjects.

The primary endpoint was the clinical response at the Test-of-cure (TOC) visit (7 to 14 days post-therapy) in the microbiological modified intent-to-treat and microbiologically evaluable co-primary populations. Clinical cure rates in the Phase 2 study at Test of Cure visit (TOC) in the microbiological intent to treat population were 83.6% (51 of 61 patients) and 96.0% (24 of 25 subjects) in the ceftolozane/tazobactam and meropenem groups, respectively. The larger difference between the treatment groups in the microbiological intent to treat population was driven by subjects with a clinical outcome of indeterminate in the ceftolozane/tazobactam arm. Clinical failure at TOC was reported for 6 patients (9.8%) in the ceftolozane/tazobactam group and for 1 patient (4.0%) in the meropenem group. Among the 6 clinical failures in the CXA-101/tazobactam group, 2 were due to post-surgical wound infection and 2 were cases of diverticular disease with perforation requiring additional antimicrobial therapy and a second surgical intervention.

Complicated Urinary Tract Infections

The sponsor conducted one Phase 2 and one Phase 3 studies. The Phase 2 study compared ceftolozane without tazobactam (CXA-101) to ceftazidime in patients with cUTI and pyelonephritis, without statistical inferences. The Phase 3 study compared ceftolozane/tazobactam to levofloxacin in patients with cUTI and pyelonephritis and was designed to show non-inferiority in composite cure (clinical plus microbiologic). Safety analysis will be presented with and without integrating Phase 2 study.

Phase 3 cUTI Study

Two identical multicenter, randomized, double-blind Phase 3 trials, CXA-cUTI-10-04 and -05 were initially planned, each with a sample size of 776 subjects. The primary objective was to compare the safety and efficacy of ceftolozane/tazobactam (1.5 g every 8 hours) administered as a 1-hour intravenous (IV) infusion to levofloxacin (750 mg once daily) administered as a 1.5-hour IV infusion in the treatment of adult subjects with cUTI, including pyelonephritis.

Following the release of FDA guidance for complicated intra-abdominal infections (cIAI) indicating that a single large study in IAI could serve as confirmatory evidence for a single cUTI study, data from the 2 identical protocols were pooled and the total sample was revised to 954 subjects (477 per arm). This sample size would achieve 90% power to demonstrate non-inferiority at a 10% margin, assuming at least 405 evaluable subjects per arm in the mMITT population, and composite clinical and microbiologic cure rate of 74% cure rate both arms.

A total of 1083 patients were randomized 1:1 at 209 study centers in 209 countries. Approximately 75% of subjects were enrolled in Eastern Europe. 543 subjects were randomized to receive ceftolozane/tazobactam 1.5 g IV every 8 hours plus one dummy infusion and 540 subjects were randomized to receive 750 mg IV levofloxacin arm plus three dummy infusions. Randomization was initially stratified by study site, and later amended to stratification by region after pooling of the two protocols. Subjects were hospitalized for the duration of the 7-day IV therapy, and those requiring urinary procedures (including removal of an indwelling catheter, bladder instrumentation, and relief on an obstruction) were allowed to receive 9 days of study treatment. At selected sites, clinically stable subjects could be discharged from the hospital after completion of at least 9 doses (3 days) of study drug if arrangements were made for continued outpatient IV administration. An unblinded pharmacist adjusted doses of the study drugs for renal insufficiency as described under section 6.2.

A urine culture was obtained within 36 hours of study drug administration. Investigators could enroll a subject before the culture results were known, but if the culture did not meet the definition of a qualifying pretreatment culture, the subject was withdrawn from the study therapy but followed for safety. Polymicrobial urine cultures in non-catheterized subjects were considered contaminated unless an isolate grew to $>10^5$ CFU/mL or was also isolated from blood culture obtained at same visit. Pre-treatment blood cultures were required in catheterized

patients. In all subjects, coagulase negative Staphylococci and non-Group D streptococci were not considered uropathogens.

Clinical and microbiologic assessments were done at EOT (within 24 hours after last dose of study drug), at the TOC visit (7 +/-2 days after the last dose of study drug) and the Late Follow Up visit (21 to 42 days after last dose of study drug). Subjects were also required to complete a Patient Symptom Questionnaire at the TOC visit.
The primary efficacy endpoint was the composite microbiological eradication and clinical cure rate in the microbiological modified intent to treat (mMITT) population at the TOC visit. The mMITT population was defined as all randomized subjects who received any amount of study drug and had at least 1 qualifying causative uropathogen from a pretreatment baseline urine specimen.

The key secondary efficacy variable was the composite microbiological eradication and clinical cure rate in the microbiologically evaluable (ME) population at the TOC visit. Noninferiority was concluded if the lower bound of the 2-sided 95% CI of the difference in composite cure was greater than -10.0% in the mMITT and in the ME populations at TOC population for the primary and key secondary efficacy endpoints, respectively.

The original protocols (dated 02 November 2010) were amended four times. The first amendment (02 January 2011, protocol version 2.0) was made to modify the primary and secondary endpoints and primary efficacy population in accordance to FDA advice and cUTI current guidance provided to the Applicant in writing on December 2nd, 2010. The time of the TOC visit was changed from 5 to 9 days to 7 (±2 days) after the last treatment dose. The inclusion criteria were modified to incorporate and describe symptoms according to FDA cUTI guidance. The second amendment, dated 25 April 2011 (protocol version 2.1), was to revise the process by which patient outcomes were collected and to provide a full description of the Patient Symptom Questionnaire. The third amendment, dated 01 April, 2013, (version 3.0) was to describe the data pooling for the FDA submission and to amend the sample size and the fourth amendment described the primary and secondary endpoints and analysis plan for non-US regulatory bodies.

Phase 2 cUTI study

This was a multicenter, double-blind, randomized study to compare the safety and efficacy of ceftolozane (without tazobactam)1000 gm IV q 8 hours and ceftazidime 1000 mg IV q 8 hours in complicated urinary tract infections, including pyelonephritis.
The primary efficacy endpoint was microbiological eradication in the microbiologically evaluable (ME) population.

A total of 129 patients were randomized 2:1 to receive either ceftolozane or ceftazidime (86 ceftolozane, 43 ceftazidime). The mMITT population included 65 subjects in the ceftolozane arm and 38 subjects in the ceftazidime arm. A higher proportion of subjects were excluded from the mMITT in the ceftolozane arm due to lack of qualifying pathogen from urine culture. The ME

population in the ceftolozane and ceftazidime arms included 55 and 27 subjects, respectively. Similar to the Phase 3 cUTI study, approximately 30% had pyelonephritis and approximately 70% had cUTI. *E. coli* was the most common uropathogen, isolated in 66.2% and 71.1% of patients in the ceftolozane and ceftazidime treatment arms, respectively, in the mMITT population. In the mMITT population, microbiological cure rates at the TOC visit were 83.1% (54/65) and 76.3% (29/38) for ceftolozane and ceftazidime treatment arms, respectively. Corresponding cure rates in the ME population were 85.5% (47/55) and 92.6% (25/27) for ceftolozane and ceftazidime treatment arms, respectively.

6 Review of Efficacy

The efficacy of ceftolozane/tazobactam was assessed as a treatment for two indications: complicated intra-abdominal infections (cIAI), discussed in Section 6.1, and complicated urinary tract infections (cUTI), discussed in Section 6.2.

Efficacy Summary

In both indications, the Phase 3 studies met their primary efficacy endpoint, demonstrating non-inferiority to the comparator based on a 10% margin.

Potential limitations of the efficacy conclusions of the pivotal clinical trials that are common to both indications included limited experience in subjects with moderate and severe renal failure and the applicability of microbiology sensitivity results given the differences of resistance patterns by regions. Additional details regarding efficacy findings and limitations of the conclusions are described below, in the summary of efficacy by indication.

cIAI indication

The main evidence of efficacy of ceftolozane/tazobactam plus metronidazole in cIAI comes from a randomized, double-blind phase 3 trial that resulted from the pooling of two original phase 3 studies and included a total sample size of 1015 subjects. The study narrowly met its primary endpoint: ceftolozane/tazobactam plus metronidazole was marginally noninferior (using a noninferiority margin of 10%) to meropenem based on the difference in clinical cure rates in the Microbiological Intent-to-Treat (MITT) population at the Test-of-Cure (TOC) visit. The key secondary endpoint, demonstrating noninferiority in the Microbiologically Evaluable (ME) population at the TOC visit, was also met within a 10% margin, with a less unfavorable margin, due to the exclusion of subjects with an indeterminate outcome, a group that was larger in the ceftolozane/tazobactam arm and which drove the differences in cure rates among treatment and comparator arms in the MITT population.

Patients with indeterminate outcomes in the ceftolozane/tazobactam plus metronidazole arm included a higher number of patients who prematurely discontinued the study drug due to adverse events and deaths and withdrawal of consent from participation for unclear reasons. Therefore, the differences in indeterminate outcomes are not a random occurrence in both

treatment arms, and, taking a conservative approach, should be considered potential treatment failures. They were counted as treatment failures in the primary endpoint analysis.

The efficacy conclusions limitations result from a study population that mostly included community-acquired intra-abdominal infections and had a relatively small percentage of severely ill patients (17% enrolled patients with infections originating from the bowel site, and 20% APACHE >10). This study population is similar to that of other trials for the same indication, presented by other applicants. One important subpopulation where experience was limited was severe renal impairment, since subjects with a creatinine clearance <15 mL were excluded from the study and those whose clearance was <30 mL discontinued the drug according to the protocol.
Given the spectrum of its antibacterial effect, the efficacy conclusions are primarily applicable to intra-abdominal infections arising from normal gut flora and where hospital-acquired pathogens, including carbapenem-resistant organisms, *Candida, Staphylococcus aureus, Enterococcus spp. or Acinetobacter spp.*, are not suspected.

Although there was little representation of patients from the United States and races other than white, there are no fundamental disease differences or other theoretical reasons why the conclusions would not be generalizable to people of the United States.

The table below shows the primary and key secondary outcomes at the TOC visit.

Table 7**:** Primary and key secondary outcomes at the TOC visit in cIAI study

	Clinical Response	Ceftolozane/ Tazobactam + Metronidazole n (%)	Meropenem n (%)	Difference (95% CI)
Primary Analysis (MITT)		N=389	N=417	
	Cure	323 (83.0)	364 (87.3)	Applicant: -4.2 (-8.91, 0.54)[1] Reviewer: -4.3 (-9.2, 0.7)[2]
	Failure	32 (8.2)	34 (8.2)	
	Indeterminate	34 (8.7)	19 (4.6)	
Key Secondary Analysis (ME)		N=275	N=321	
	Cure	259 (94.2)	304 (94.7)	Applicant: -1.0 (-4.52, 2.59)[1] Reviewer: -0.5 (-4.5, 3.2)[2]
	Failure	16 (5.8)	17 (5.3)	

[1] 95% CI calculated as a 95% stratified Newcombe CIs with Minimum Risk weights.
[2] 95% CI calculated as unstratified Wilson Score CIs.
Source: Statistical Reviewer Table

Several sensitivity analyses were performed to determine the influence of confounding factors over the primary outcome, such as use of prior and concomitant antibacterial agents, need for additional procedures to control the infection after 72 hours, reclassification of cures according to adequate infection source control by the surgical review panel and the effect of the removal of participants of two sites closed during the study before unblinding. All these factors affected both treatment arms in comparable ways; therefore treatment differences were not significantly affected and the CI remained within a 10% margin. From the subgroup analyses, ceftolozane/tazobactam plus metronidazole had lower point estimates of cure rates across all groups. Wider differences of >10% lower cure rates versus meropenem were observed in patients older than 65 years old, in those with an APACHE score >10 at baseline, and in those with a creatinine clearance <50mL/min. The applicant argues that, since the cure rate differences in the group of subjects older than 75 years old were not as pronounced (69.3% in ceftolozane/tazobactam plus metronidazole versus 73% in meropenem), the wider difference in the overall cohort of subjects >65 years old is driven by a random occurrence of lower cure rates in the cohort of subjects >65 years to <75 years old.

However, this observation is based on the analysis of a smaller subgroup within a subgroup and therefore has more limitations than the analysis of the whole cohort of subjects older than 65 years of age. In addition, the >75 year old group in the ceftolozane/tazobactam plus metronidazole arm also had a higher number of failures and the highest number of deaths (7 of the total 11 deaths) observed in this arm.

Clinical cure rates by region were similar in Eastern Europe and Latin America, which enrolled the highest number of subjects. In Western Europe, North America and Rest of the World, cure rates were overall >10% lower and had wide confidence intervals due to the small sample sizes. Baseline risk factors were comparable among all regions.

In the phase 3 trial, 11/482 (2.3%) and 8/497 (1.6%) subjects died in the ceftolozane/tazobactam plus metronidazole arm and meropenem arm, respectively. All deaths occurred within 32 days of study start in both treatment arms and were the result of worsening and/or complications of infection, surgery and underlying conditions. They were not considered drug related. However, lack of treatment efficacy cannot be excluded as a contributing factor.

The supportive evidence provided by the phase 2 trial had the limitations of a shorter duration of therapy (4 to 7 days), an earlier time point for assessment of outcomes (7 to 14 days), a smaller sample size (121 subjects), and a 2:1 randomization. Key point estimates in this trial were also substantially lower in the ceftolozane/tazobactam arm (cure rates of 83% vs. 96% in the meropenem arm). Estimation of mortality rates from both phase 2 and 3 trials showed a slight imbalance at 14/564 (2.5%) vs. 8/545 (1.5%). Adjusting for the difference in size of the trials, the weighted treatment difference was 1.0% (95% CI: -0.9%, 2.8%). Deaths in the phase 2 trial also represented treatment failures due to worsening and/or complications of infection and underlying conditions. Cure rates by baseline pathogens were generally similar across both treatment arms for all Enterobacteriaceae. Lower cure rates in ceftolozane/tazobactam plus metronidazole patients with *Streptococcus anginosus* at baseline were noted at 25/30 (83.3%) vs.

23/23 (100%) for patients treated with meropenem. In the subgroup of polymicrobial infections, a lower efficacy (percentage difference of -7.2 in the clinical cure rate) was observed for ceftolozane/tazobactam plus metronidazole compared with meropenem. The clinical evaluation of efficacy of ceftolozane/tazobactam against anaerobes was limited by the concomitant use of metronidazole, which provided anaerobic coverage. However, based on the in vitro susceptibility data, most of the *Bacteroides fragilis* from the study were sensitive to ceftolozane/tazobactam. Other *Bacteroides* spp. were resistant.

Following 10 days of study therapy, the incidence of emergent infections was low and included mainly new infections with organisms intrinsically resistant to cephalosporin therapy (*Enterococcus spp*. and *Staphylococcus spp*.).

Based on the current results, dose ranging studies exploring the safety and efficacy of a higher dose in elderly subjects would be very informative, and I suggest that it be recommended as a post-marketing commitment.

cUTI indication

The primary efficacy evidence in support of the cUTI indication was a randomized, double-blind phase 3 trial that resulted from the pooling of two original phase 3 studies, with a final sample size of 1083 patients. Ceftolozane/tazobactam met the primary efficacy endpoint, demonstrating non inferiority to levofloxacin with respect to the composite microbiological and clinical cure rates at the TOC visit within a 10% margin in the modified microbiological intention-to-treat population (mMITT), comprised of randomized subjects who received a single dose of study drug and had a microbiologically confirmed infection from a specimen taken prior to study drug administration. The table below shows the breakdown of the outcomes at the TOC visit in the mMITT population and their respective confidence intervals.

Table 8: Composite Cure at TOC visit – mMITT – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 398	Levofloxacin N = 402	Difference (95% CI)
Composite Cure	306 (76.9%)	275 (68.6%)	8.5 (2.31, 14.57)*
Failure	66 (16.6%)	103 (25.6%)	
Indeterminate	26 (6.5%)	24 (6.0%)	

*The 99% CI for the difference was (0.36, 16.46)

The 99%CI for the difference in composite cure indicated that ceftolozane/tazobactam was superior to levofloxacin in the treatment of cUTI and pyelonephritis. Ceftolozane/tazobactam was also superior for clinical and microbiologic cure individually. The prevalence of baseline resistance to levofloxacin among gram negative isolates was high in each arm (25-28%), whereas the prevalence of baseline resistance to ceftolozane/tazobactam was 3%. Approximately 97% of subjects who received ceftolozane/tazobactam had an organism that was susceptible to ceftolozane/tazobactam, while 72% of subjects in the levofloxacin arm had an organism

susceptible to levofloxacin. Among subjects with a levofloxacin resistant organism, ceftolozane/tazobactam was superior to levofloxacin. Among subjects with levofloxacin susceptible organisms, ceftolozane/tazobactam was non-inferior to levofloxacin for the composite cure and also non-inferior for the individual components of microbiologic and clinical cure. The superiority finding in the overall population was due to and driven by the superiority of ceftolozane/tazobactam in the subset of subjects infected with levofloxacin resistant organisms at baseline.

Clinical cure was similar in the subset of subjects with pyelonephritis or cUTI. For microbiologic cure, ceftolozane/tazobactam seemed superior in the subpopulation of subjects with cUTI, and similar in the subpopulation with pyelonephritis. This is explained by the prevalence of levofloxacin resistance at baseline, which was higher among cUTI subjects compared to pyelonephritis subjects (44.5% vs. 22.2%). The composite cure was consistently numerically higher in all subgroups and across all regions except in North America where levofloxacin had a higher numerical response. The number of enrolled subjects in North America was small (25 total, 14 in US and 11 in Mexico), and there are no clear theoretical reasons that are likely to impact the applicability of foreign data to the US population.

Ceftolozane/tazobactam achieved a greater response compared to levofloxacin in the subgroup of *Enterobacteriaceae* that were ESBL producers. This finding can be explained by the high prevalence of levofloxacin resistance among ESBL isolates at baseline, compared to the prevalence of ceftolozane resistance at baseline. However, the higher cure rates in ESBL producers indicate that ceftolozane is an alternative to other therapies in patients infected with these organisms.
The frequency of emergence of organisms with decreased susceptibility or resistance to ceftolozane/tazobactam was lower compared to levofloxacin. *Enterococcus spp*., which are intrinsically resistant to ceftolozane/tazobactam, were the main pathogens that resulted in superinfections or new infections.

6.1 Treatment of Complicated Intra-abdominal Infections

The applicant is seeking an indication for cIAI as follows:

ZERBAXA used in combination with metronidazole is indicated for the treatment of complicated intra-abdominal infections caused by the following Gram-negative and Gram-positive microorganisms: *Enterobacter cloacae, Escherichia coli* (b) (4) *Klebsiella oxytoca, Klebsiella pneumoniae* (b) (4) *Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis,* (b) (4) *Streptococcus anginosus, Streptococcus constellatus*, and *Streptococcus salivarius*.

Complicated Intra-abdominal Infections
Infections within the abdominal cavity are usually polymicrobial and include peritonitis, which may be generalized or localized (phlegmon), and intraabdominal abscess. These infections

usually arise after a breach in the normal mucosal defense barrier (appendicitis, diverticulitis, carcinoma of the colon, inflammatory bowel disease, and previous colon surgery) that allows the entry of an inoculum composed of the normal intestinal flora. In the community acquired type of infection, the predominant bacteria are Gram negative bacteria, Gram positive streptococci/enterococci, and anaerobic bacteria. The predominant isolates in most series are *B. fragilis* and *E. coli.* As antimicrobial therapy is generally initiated before culture results are available, the antimicrobial therapy chosen must cover Gram-positive and Gram-negative aerobic and anaerobic bacteria that comprise the usual gastrointestinal flora.

6.1.1 Methods

The applicant performed two controlled and randomized, multicenter Phase 3 trials with identical study design pooled into one study. Please refer to Section 5.3 for a description of the data pooling of these two studies and an overview of the study design. In the subsections below, the methodology used in the study is discussed in more detail.

Study Objectives *(copied verbatim from the protocol)*

Primary Objective:

- To demonstrate the non-inferiority of CXA-201 and metronidazole vs. meropenem in adult subjects with complicated intraabdominal infection (cIAI) based on the 95% confidence interval (CI) around the difference in clinical cure rates at the TOC visit (26 to 30 days after the initiation of study drug administration) in the microbiological intent-to-treat (MITT) population.

Secondary Objective(s):

- To demonstrate the non-inferiority of CXA-201 and metronidazole vs. meropenem in adult subjects with cIAI based on the 95% CI around the difference in clinical cure rates at the TOC visit (26 to 30 days after the initiation of study drug administration) in the microbiologically evaluable (ME) population.
- To compare the clinical response of CXA-201 and metronidazole to that of meropenem at the TOC visit in the clinically evaluable (CE) population.
- To compare the microbiological response of CXA-201 and metronidazole to that of meropenem at the TOC visit.
- To compare the clinical and microbiological responses of CXA-201 and metronidazole versus meropenem at the EOT (within 24 hours of last dose of treatment) and LFU visit (38-45 days post first dose of study drug)
- To evaluate the safety and tolerability of CXA-201 in adult subjects with cIAI.

Inclusion Criteria *(copied verbatim from the protocol)*

Subjects **MUST** satisfy all of the following entry criteria before they will be allowed to participate in the study:

1. Provide written informed consent prior to any study-related procedure not part of normal medical care (a legally acceptable representative may provide consent if the subject is unable to do so, provided this is approved by local country and institution specific guidelines).
2. Be males or females ≥ 18 years of age.
3. If female, subject is non-lactating, and is either:
    a. Not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile due to bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or
    b. Of childbearing potential and is practicing a barrier method of birth control (e.g., a diaphragm or contraceptive sponge) along with 1 of the following methods: oral or parenteral contraceptives (oral or parenteral contraceptives must have been used for at least 3 months prior to study drug administration), or a vasectomized partner. Or, the subject is practicing abstinence from
    sexual intercourse. Subjects must be willing to practice these methods for the duration of the trial and for at least 35 days after last dose of study
    medication.

4. Males are required to practice reliable birth control methods (condom or other barrier device) during the conduct of the study and for at least 35 days after last dose of study medication.
5. One of the following diagnoses (in which there is evidence of intraperitoneal infection):
    a. Cholecystitis (including gangrenous cholecystitis) with rupture, perforation, or progression of the infection beyond the gallbladder wall;
    b. Diverticular disease with perforation or abscess;
    c. Appendiceal perforation or periappendiceal abscess;
    d. Acute gastric or duodenal perforation, only if operated on > 24 hours after perforation occurs;
    e. Traumatic perforation of the intestine, only if operated on > 12 hours after perforation occurs;
    f. Peritonitis due to other perforated viscus or following a prior operative procedure;
    i. Subjects with inflammatory bowel disease or ischemic bowel disease are eligible provided there is bowel perforation.
    g. Intraabdominal abscess (including liver or spleen); or
6. Subject requires surgical intervention (e.g., laparotomy, laparoscopic surgery, or percutaneous draining of an abscess) within 24 hours of (before or after) the first dose of study drug.
7. If subject is to be enrolled preoperatively, the subject should have radiographic evidence of bowel perforation or intraabdominal abscess.
8. Subjects who failed prior antibacterial treatment for the current cIAI can be enrolled but must: (a) have a positive culture (from an intraabdominal site) and (b) require surgical intervention. Such subjects can be enrolled before the results of the culture are known; however, if the culture is negative, study drug administration must be discontinued.
9. Willing and able to comply with all study procedures and restrictions.
10. Evidence of systemic infection including one or more of the following:
    a. Temperature (oral) greater than 38 °C or less than 35 °C;
    b. Elevated WBC (>10,500/mm3);
    c. Abdominal pain, flank pain, or pain likely due to cIAI that is referred to another anatomic area such as back or hip; or
    d. Nausea or vomiting.
11. Collection of a baseline intra-abdominal specimen in compliance with protocol Section 9.1. Screening/Baseline (pre-operative enrollment and dosing is acceptable, provided that the sample from the site of infection is obtained during the interventional procedure).

Exclusion Criteria *(copied verbatim from the protocol)*
If any of the following apply, the subject **MUST NOT** enter the study:
1. Diagnosis of abdominal wall abscess; small bowel obstruction or ischemic bowel disease without perforation.
2. Simple appendicitis; acute suppurative cholangitis; infected necrotizing pancreatitis; pancreatic abscess; or pelvic infections.
3. Spontaneous [primary] bacterial peritonitis associated with cirrhosis and chronic ascites.

4. Complicated intraabdominal infection managed by staged abdominal repair (STAR), open abdomen technique (i.e., fascia not closed) including temporary closure of the abdomen, or any situation where infection source control is not likely to be achieved.
5. Known prior to randomization to have an IAI or postoperative infection caused by pathogen(s) resistant to meropenem.
6. Use of systemic antibiotic therapy for IAI for more than 24 hours prior to the first dose of study drug, unless there is a documented treatment failure with such therapy.
7. More than one dose of an active non-study antibacterial regimen given postoperatively. For subjects enrolled preoperatively, no postoperative non-study antibacterial therapy is allowed.
8. Subjects who previously received imipenem, meropenem, doripenem or cefepime for the current intraabdominal infection.
9. Have a concomitant infection at the time of randomization, which requires non-study systemic antibacterial therapy in addition to IV study drug therapy. (Drugs with only gram-positive activity [e.g., daptomycin, vancomycin, linezolid] are allowed).
10. Severe impairment of renal function (estimated CrCl < 30 mL/min), or requirement for peritoneal dialysis, hemodialysis or hemofiltration, or oliguria (< 20 mL/h urine output over 24 hours).
11. The presence of hepatic disease at baseline as defined by any of the following:
    a. ALT (SGPT) or AST (SGOT) > 4 x upper limit of normal (ULN)
    b. Total bilirubin > 2 x ULN, unrelated to cholecystitis
    c. Alkaline phosphatase > 4 x ULN. Subjects with a value > 4 x ULN and < 5 x ULN are eligible if this value is historically stable
    d. Acute or chronic hepatitis, cirrhosis, acute hepatic failure, acute decompensation of chronic hepatic failure.
12. Hematocrit < 25% or hemoglobin < 8 gm/dL.
13. Neutropenia with absolute neutrophil count < 1000 /mm3.
14. Platelet count < 75,000 /mm3. Subjects with a platelet count as low as 50,000 /mm3 are permitted if the reduction is historically stable.
15. Considered unlikely to survive the 4- to 5-week study period.
16. Any rapidly-progressing disease or immediately life-threatening illness (including respiratory failure and septic shock).
17. Immunocompromising condition, including established Acquired Immune Deficiency Syndrome (AIDS), hematological malignancy, or bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, or the administration of corticosteroids equivalent to or greater than 40 mg of prednisone per day administered continuously for more than 14 days preceding randomization.
18. Have a documented history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam antibacterial (a history of a mild rash followed by uneventful re-exposure is not a contraindication to enrollment), including cephalosporins, carbapenems, penicillins, or ß-lactamase inhibitors, or metronidazole, or nitroimidazole derivatives.
19. Any condition or circumstance that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of study data.

20. Participation in any clinical study of an investigational product within 30 days prior to the proposed first day of study drug.
21. Previous participation in any study of CXA-101 or CXA-201.
22. Subjects who have received disulfiram in the past 14 days or who are currently receiving probenecid.
23. Women who are pregnant or nursing.

Reviewer's comments: the eligibility criteria are adequate to select the appropriate patient population to assess the study endpoints. They adhere to recommendations of the FDA draft guidance on intra-abdominal infections that was available. The schedule of assessments is adequate to evaluate safety and efficacy endpoints.

Concomitant Medications *(copied verbatim from the protocol)*

Prior administration of systemic antibacterial agents for treatment of the current IAI is allowed only in the following circumstances:

- Subjects with new infections (not considered to have failed a previous regimen), including those with postoperative infections;
- Treatment for < 24 hours before the first dose of study drug that would not be expected to eradicate the infection; and
- No more than one dose of an antibacterial regimen active against the baseline pathogen was given postoperatively in a subject randomized postoperatively.

1. Subjects randomized pre-operatively may not receive any postoperative non-study antibacterial therapy;
OR
Subjects considered to have failed a previous antibiotic regimen (other than a carbapenem), received prior administration of a non-study systemic antibacterial therapy for peritonitis or abscess are permitted provided all of the following criteria are met:

- The treatment was given for at least 48 hours;
- The original pathogen(s) (if isolated and tested) was susceptible to meropenem
- There are clinical and operative or radiographic findings clearly indicating ongoing infection;
- Operative intervention or re-intervention (if previous surgical procedure) is intended no more than 24 hours after first dose of study drug;
- No further non-study antibiotics are administered postoperatively; and
- Current positive baseline bacterial culture from intraabdominal site.

Specimens for bacterial culture and susceptibility testing should be taken at operative intervention. Culture results do not need to be known before randomization but if the culture is subsequently found to be negative, the subject will be considered to have undocumented evidence of treatment failure and must be withdrawn from study drug. It may be useful to obtain a Gram-stain of fluid from the site of infection; if there are minimal WBCs and no or rare bacteria seen, the likelihood of a positive culture is low and such a subject should usually not be enrolled.

Concomitant systemic antibacterial therapy is not permitted, with exception of linezolid, daptomycin or vancomycin, for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Enterococcus*. If there is a need for concomitant systemic antibacterial therapy (other than that allowed above) for the current IAI or any other infection, the subject must be withdrawn from study drug treatment.
Daptomycin, vancomycin, or linezolid may be administered if required for documented MRSA infection. If added, daptomycin, vancomycin, or linezolid should be used according to the product label and institutional guidelines. Note: Empiric therapy for *Enterococcus* is not necessary for community-acquired infections but could be considered in hospital-acquired infections or in subjects with high severity illness (defined as APACHE II score > 15).

Study Treatments

Patients were randomized 1:1 to receive ceftolozane/tazobactam (1.5 g every 8 hours) plus metronidazole (500 mg every 8 hours) or meropenem (1 g every 8 hours) with placebo (every 8 hours) for 4 to 10 days. Treatment could be extended beyond Day 10 if there were any of the following: multiple abscesses, diffuse peritonitis from a source other than the appendix, failure of prior therapy and a source other than the appendix, or hospital acquired infection. Hospitalization was mandatory for at least the first 9 doses (approximately 3 days).

Subjects received 6 daily infusions (6 active infusions in the ceftolozane/tazobactam plus metronidazole treatment arm or 3 active infusions and 3 dummy saline infusions to maintain the blind in the meropenem treatment arm.

Dose adjustments for renal function were done as follows:

For Subjects randomized to Ceftolozane/tazobactam plus metronidazole:
CrCl > 50 mL/min: No dose adjustment required
CrCl 30 – 50 mL/min: Decrease ceftolozane/tazobactam dose to 750 mg IV q8h (± 2 hours)
CrCl < 30 mL/min: Discontinue study drug
Note: 750 mg ceftolozane/tazobactam = 500 mg/250 mg of ceftolozane/tazobactam
No changes to the metronidazole dose are required for renal insufficiency.

For Subjects randomized to meropenem:
CrCl > 50 mL/min: No dose adjustment required
CrCl 30 – 50 mL/min: Decrease meropenem dose to 1000 mg IV q12h (± 2 hours) CrCl < 30 mL/min: Discontinue study drug

Schedule of Visits and Clinical Assessments

Clinical assessments were performed at the Screening (Baseline; Day -1 to Day 1 before dosing); during treatment (Day 1 to Day 10), at the EOT visit within 24 hours after the last dose of study

drug, at the TOC visit 26 to 30 days after the first dose of study drug, and the LFU visit 38 to 45 days after the first dose of study drug).

At the Screening visit, intra-abdominal specimens were collected for culture of both aerobes and anaerobes at the time of the initial interventional procedure (within 24 hours of study drug administration). Blood samples for culture were drawn in subjects with hospital-acquired infections, those who had failed prior antibacterial therapy, or those who had signs of severe sepsis. A thorough physical exam and radiological evidence of intra-abdominal infection was conducted. Subjects enrolled pre-operatively must have had a radiological exam confirming cIAI. Laboratory tests for determination of inclusion/exclusion criteria and renal function dosage adjustments were performed at the local site laboratory and all safety labs were done at a central lab. During treatment, clinical and laboratory assessments were done (please refer to the schedule of assessment table below). Subjects had a minimum of 4 days of intravenous study drug treatment. 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. Each randomized subject had 6 scheduled doses of study drug (3 doses of ceftolozane/tazobactam plus 3 doses of metronidazole or 3 doses of meropenem plus 3 doses of placebo) for a total of 6 infusions at 8-hour intervals each day. At the EOT visit, the investigator performed a targeted clinical exam and the assessment of clinical response. AEs were reviewed and blood was drawn for safety labs. At the TOC visit (at 26 to 30 days after the first dose of study drug), assessment of AEs and safety labs, physical exam and assessment of clinical response was performed by the investigator. Microbiological specimens were obtained when necessary.
The LFU visit occurred 38-45 days after the first dose of study drug. The LFU could be conducted by a telephone interview, unless there were clinical or laboratory findings suggestive of persistent infection or if the subject had missed the TOC visit.

Table 9: Schedule of Assessments

	Scheduled Assessment or Procedure	Study Day							
		-1 to 1 (Baseline)	1	2[1]	3[1]	4-10[1]	EOT	26 to 30 TOC[2]	38 to 45 LFU[2,3]
	Informed consent	X							
	Inclusion/exclusion criteria	X							
	Medical and surgical history	X							
	Calculate APACHE II Score	X							
	Randomization		X						
Central Laboratory	Blood for coagulation, hematology, and chemistry evaluations (local results should be used for baseline qualification)	X			X		X	X	X[4]
Central Laboratory	Site of infection sample for culture	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Central Laboratory	Urinalysis and urine microscopy	X			X[4]		X[4]	X[4]	X[4]
Central Laboratory	Coombs test (direct)	X					X		
Local Laboratory	Serum pregnancy test	X						X	
Local Laboratory	Draw creatinine and estimate creatinine clearance	X		X[4]	X[4]	X[4]			
Local Laboratory	Blood for culture	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Clinical	Vital signs and temperature	X	X	X	X	X	X	X	
Clinical	Complete physical examination	X							
Clinical	Targeted physical examination						X	X	
Clinical	Height and weight measurement	X							
Clinical	Prior and/or concomitant medications	X	X	X	X	X	X	X	X
Clinical	Record radiologic exam	X[5]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Clinical	Record any procedures, including blood or blood product transfusions	X	X	X	X	X	X	X	X
Clinical	Record summary of operative procedures and operative notes	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Clinical	Abdominal symptoms and signs, and wound assessments	X	X	X	X	X	X	X	X[4]
Clinical	Assess for AEs		X	X	X	X	X	X	X
Clinical	Assess clinical outcome						X	X	X[4]
Clinical	CXA-201 and metronidazole or comparator (meropenem) IV infusion		X	X	X	X[4]			
Clinical	Determine need for continued therapy					X			

Abbreviations: EOT = End-of-Therapy; TOC = Test-of-Cure; LFU = Late Follow-up.
1. For Study Days 2 through 10 all study assessments should be consistently conducted for each study day (e.g., every morning).
2 For TOC and LFU, days indicated are the number of days after administration of the first dose of study drug.
3 LFU can be conducted by telephone or other interactive technology if subject had a TOC visit with no laboratory abnormalities requiring follow-up assessment.
4 When clinically indicated
5 Required if subject is to be randomized pre-operatively

The LFU visit assessments included evaluation of sustained clinical response, microbiological response, assessment of the subject's current cIAI symptoms, and safety laboratory assessments.

Microbiological Assessments

Baseline microbiological specimens based on specimen- and organism-specific protocols were obtained at baseline.
Culture and susceptibility testing were performed at local and regional laboratories, as applicable. All isolates were sent to the central laboratory for verification of identification and susceptibility. Any isolate was identified to the genus and species level at the central laboratory.

Susceptibility testing of all isolates from sputum, pleural fluid, and blood were performed in the central laboratory using broth microdilution and Kirby-Bauer disk diffusion tests.

Analysis Populations *(copied verbatim from the protocol)*

Intent-to-Treat (ITT) Population
The intent-to-treat (ITT) population will consist of all randomized subjects.

Microbiological Intent-to-Treat (MITT) Population
The MITT population will consist of all randomized subjects who have IAI as evidenced by identification of a baseline intraabdominal pathogen, regardless of susceptibility to study drug. Subjects in the MITT population will be categorized based on the treatment that subjects were randomized to, irrespective of what they actually received.

Clinically Evaluable (CE) at TOC Population
The CE population consists of subjects who meet the protocol definition of cIAI, who adhere to study procedures and have a clinical outcome at the TOC visit. Further specific details defining this population will be described in the statistical analysis plan.

Microbiologically Evaluable (ME) at TOC Population
The ME population is the subset of CE subjects who have at least one baseline intraabdominal pathogen identified that is susceptible to study drug.

Clinically Evaluable at Late Follow-Up (CE at LFU) Population
The CE at LFU population will be a subset of the CE at TOC population and includes all subjects who are clinical cures at the TOC visit, adhere to study procedures and have an LFU assessment (or are classified as a clinical failure prior to the LFU visit).

Safety Population
All safety analyses were performed in the safety population, which included all subjects who received any amount of the study drug. Subjects in the safety population were categorized based on the actual treatment that subjects received, irrespective of the treatment to which they were randomized.

Outcome Measures

Clinical Outcomes
Clinical response was classified by the investigator as *Clinical Cure, Clinical Failure, or Indeterminate*. Patients determined to be a *Clinical Failure* at the EOT were carried forward to the TOC and LFU visits. Patients classified as *Clinical Cure* at the TOC were also classified as *Clinical Cure* at the EOT. Missing outcomes at the TOC were imputed as *Clinical Failures* for the primary endpoint analysis. The table below shows the definitions of clinical responses. The following outcomes were assessed at the TOC visit:

Table 10: Outcomes measured at the TOC visit in cIAI

Outcome	Definition
Clinical Cure	Complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antibacterial therapy or surgical drainage procedure is required for the index infection.
Clinical Failure	• Death related to IAI at any time point prior to the TOC • Persisting or recurrent infection within the abdomen requiring additional intervention to cure the infection* • Need for treatment with additional antibiotics for ongoing symptoms of IAI prior to the TOC, or • Post-surgical wound infection, defined as an open wound with signs of local infection, such as purulent exudate, erythema, or warmth that requires additional antimicrobial therapy and/or non-routine wound care (such as incision and drainage or re-opening of the wound).** Note: Closure of a colostomy or an enterocutaneous fistula is not considered a failure. Wherever possible, failures should be documented microbiologically by obtaining an appropriate deep wound or intraabdominal site culture. Blood cultures should also be obtained. * Repeat percutaneous aspiration of an abscess within 72 hours of the original aspiration, without worsening clinical signs and symptoms, is not considered a failure. However, the need to repeat any procedure after 72 hours of study therapy to cure the infection should be considered a failure. Exploratory or diagnostic procedures with no evidence of an ongoing infection are not considered a failure. **Use of vacuum-assisted wound closure following fascial closure is acceptable and such procedure must be reported on the abdominal intervention page. Daily wound assessments must be conducted according to schedule of events.
Indeterminate	Study data are not available for evaluation of efficacy for any reason, including death during the study period unrelated to the index infection, or Extenuating circumstances that preclude classifications as cures or failure (e.g., Subject Lost to follow-up)

Microbiological Outcomes

Per Subject Microbiological Outcomes: The applicant determined an overall microbiological response for each subject based on individual microbiological responses for each baseline pathogen at both the EOT and TOC visits. In order for the subject to have a favorable overall microbiological response (i.e., success), each baseline pathogen must have had a favorable microbiological outcome. If the outcome for any pathogen was unfavorable, the subject was considered an overall microbiological failure.

Per Pathogen Microbiological Outcomes: The applicant determined a microbiological response for each pathogen isolated at baseline at both the EOT and TOC visits. Microbiological response categories were eradication, presumed eradication, persistence, persistence acquiring resistance, presumed persistence, and indeterminate. Favorable microbiological responses included "eradication" or "presumed eradication." Unfavorable responses were considered "persistence," "persistence acquiring resistance," and "presumed persistence."

Efficacy Endpoints

The primary efficacy endpoint was the clinical cure rate at the TOC visit in the primary MITT population.

The key secondary efficacy endpoint was the clinical cure rate at the TOC visit in ME population. Additional secondary endpoints were:

- Clinical cure rate at the TOC visit in the CE population.
- Microbiological eradication rates (per-subject) at the TOC visit in the ME population.
- Per-pathogen microbiologic eradication rates at the TOC visit in the ME population.
- Proportion of subjects with a superinfection or a new infection in the MITT population.

Statistical Methods

The primary statistical goal of the study was to establish non-inferiority of ceftolozane/tazobactam plus metronidazole to meropenem with respect to proportion of subjects in the MITT primary analysis population who achieve clinical cure at TOC visit.
The lower limit of the 95% confidence interval (CI) for the difference in the proportions of patients with clinical cure was obtained. Non-inferiority was demonstrated if the lower limit of the 95% CI was greater than -10 using a 2-sided significance level of 0.05 for statistical significance of the test of non-inferiority.

Non-Inferiority Margin Justification:
The 95%-95% fixed margin approach was used to justify the non-inferiority 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 source data were obtained from an extensive review of the medical literature. 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=15.60%), taking a conservative approach, the clinically relevant non-inferiority margin (M2) of 10.0% still ensures the preservation of approximately 36.0% of the active control effect.

Randomization and Stratification

Subjects were assigned to treatment in a 1:1 randomization ratio by using an interactive voice response system/interactive web response system (IVRS/IWRS), stratified by geographical

region and primary site of infection with 2 levels: bowel (small or large) versus other site of IAI, within each protocol.

Sample Size Calculations

A total planned sample size of 988 subjects (494 per treatment arm) when the 2 studies (CXA-cIAI-10-08 and CXA-cIAI-10-09) were combined was expected to result in approximately 395 MITT subjects per treatment arm. The planned sample size of 988 subjects ensured a minimum of 90% power to demonstrate the non-inferiority of ceftolozane/tazobactam and metronidazole to meropenem at a 10% non-inferiority margin and 1-sided significance level of 0.025 in the MITT population. These calculations assumed 80% of randomized subjects would meet the criteria to be included in the MITT population and that the clinical cure rate in both arms would be 75%. For safety evaluation, the planned sample size allowed for the following assumptions: if no SAEs were observed among 494 subjects in the treatment arm, this study provided 97.5% confidence that the true proportion of subjects with SAEs is <0.74%. If the incidence rate of a SAE was 0.38%, then there was an 85% chance of observing at least 1 such SAE among 494 subjects in the treatment arm. If the incidence rate was 0.14%, there was a 50% chance of observing at least 1 SAE.

Handling of missing data

For the primary efficacy outcome measure in the MITT population (per-subject clinical cure rate at the TOC visit), a subject with a missing TOC outcome assessment was classified as an indeterminate, but excluded in the per-protocol populations (ME, CE, and Expanded ME). Missing data for secondary efficacy outcomes were handled similarly.

6.1.2 Demographics

Demographic characteristics
The Tables 11 and 12 below show baseline characteristics of the safety and MITT populations, respectively. These were the populations for the primary safety and efficacy analyses. The intent-to-treat population (ITT) is not shown, however, it did not differ substantially from the safety population and it was comparable in both treatment arms.

Table 11**:** Baseline Characteristics in cIAI subjects Safety Population
(Reviewer's table with JMP, Subject Level Analysis and Demographic datasets)

	Ceftolozane/Tazobactam + Metronidazole N=482 n (%)	**Meropenem N=497 n (%)**
Age (years)		
>=18 and <65	366 (75.9%)	393 (79%)
>=65 and <75	60 (12.4%)	62 (12.4%)
>= 75	56 (11.6%)	42 (8.4%)

Sex		
Female	206 (42.7%)	195 (39.2%)
Male	276 (57.2%)	302 (60.7%)
Race		
Asian	13 (2.6%)	18 (3.6%)
Black or African American	4 (0.8%)	2 (0.4%)
Not Applicable	2 (0.4%)	0
Other	9 (1.8%)	11 (2.2%)
White	454 (94.1%)	466 (93.7%)
Region		
Eastern Europe	360 (74.6%)	364 (73.2%)
North America	37 (7.6%)	35 (7%)
Rest of the World	23 (4.7%)	23 (4.6%)
South America	48 (9.9%)	56 (11.2%)
Western Europe	14 (2.9%)	19 (3.8%)
Site of Infection		
Bowel (small or large)	84 (17.4%)	88 (17.7%)
Other site of IAI	398 (82.5%)	409 (82.2%)
Baseline Creatinine		
>= 30 - < 50 mL/min (moderate impairment)	26 (5.3%)	16 (3.2%)
>= 50 - < 80 mL/min (mild impairment)	118 (24.4%)	127 (25.5%)
>= 80 mL/min (normal)	338 (70.1%)	354 (71.2%)
Procedure Type		
Laparoscopy	113 (23.4%)	132 (26.5%)
Laparotomy	326 (67.6%)	314 (63.1%)
Other	7 (1.4%)	5 (1%)
Percutaneous Aspiration	36 (8.5%)	45 (9%)
APACHE Score at Baseline		
< 10	388 (80.4%)	413 (83%)
>= 10	93 (19.2%)	84 (16.9%)
Prior Antibacterial Use		
Yes	289 (59.9%)	289 (58.1%)
No	193 (40.0%)	208 (41.8%)
BMI		
<25	199 (41.2%)	190 (38.2%)
26-30	165 (34.2%)	179 (36.0%)
>30	114 (23.6%)	127 (25.5%)
Abscess Type		
Multiple	42 (8.7%)	37 (7.4%)

Single	228 (47.3%)	241 (48.4%)
Peritonitis Type		
No peritonitis	80 (16.6%)	94 (18.9%)
Local	228 (47.3%)	238 (47.8%)
Diffuse	174 (36.1%)	165 (33.2%)
Presence of Bacteremia		
No	473 (98.1%)	484 (97.3%)
Yes	9 (1.8%)	13 (2.6%)
Number of Baseline Pathogens		
Monomicrobial	137 (28.4%)	129 (25.9%)
Polymicrobial	259 (53.7%)	296 (59.5%)
Abdominal Intervention relative to randomization		
Abdominal Intervention After Randomization Abdominal Intervention Prior to Randomization	27 (5.6%) 455 (94.3%)	34 (6.8%) 463 (93.1%)

Table 12: Baseline Characteristics in cIAI subjects MITT Population
(Reviewer's table with JMP, Subject Level Analysis and Demographic datasets)

	Ceftolozane/Tazobactam + Metronidazole N=389 n (%)	**Meropenem N=417 n (%)**
Age		
>=18 and <65	289 (74.2%)	332 (79.6%)
>=65 and <75	54 (13.8%)	48 (11.5%)
>= 75	46 (11.8%)	37 (8.8%)
Sex		
Female	171 (43.9%)	169 (40.5%)
Male	218 (56.0%)	248 (59.4%)
Race		
Asian	12 (3.0%)	15 (3.6%)
Black or African American	3 (0.7%)	2 (0.4%)
Not Applicable	0 (0%)	1 (0.2%)
Other	7 (1.8%)	11 (2.6%)
White	367 (94.3%)	388 (93.0%)
Region		
Eastern Europe	297 (76.3%)	308 (73.8%)
North America	26 (6.6%)	25 (6.0%)
Rest of the World	19 (4.8%)	20 (4.8%)
South America	36 (9.2%)	45 (10.7%)
Western Europe	11 (2.8%)	19 (4.5%)

Site of Infection		
Bowel (small or large)	77 (19.7%)	80 (19.1%)
Other site of IAI	312 (80.2%)	337 (80.8%)
Baseline Creatinine		
>= 30 - < 50 mL/min (moderate impairment)	23 (5.9%)	13 (3.1%)
>= 50 - < 80 mL/min (mild impairment)	98 (25.1%)	109 (26.1%)
>= 80 mL/min (normal)	268 (68.8%)	295 (70.7%)
Procedure Type		
Laparoscopy	86 (22.1%)	104 (24.9%)
Laparotomy	274 (70.4%)	271 (64.9%)
Other	5 (1.2%)	4 (0.9%)
Percutaneous Aspiration	24 (6.1%)	37 (8.9%)
APACHE Score at Baseline		
< 10	310 (79.6%)	347 (83.2%)
>= 10	78 (20.0%)	70 (16.7%)
Prior Antibacterial Use		
Yes	224 (57.5%)	239 (57.3%)
No	165 (42.4%)	178 (42.6%)
BMI		
<25	169 (43.44%)	164 (39.33%)
26 to 30	129 (33.16%)	145 (34.77%)
>30	88 (22.62%)	107 (25.66%)
Abscess Type		
Multiple	33 (8.4%)	32 (7.4%)
Single	186 (47.5%)	208 (50.2%)
Peritonitis Type		
No peritonitis	52 (13.3%)	77 (18.4%)
Local	198 (50.9%)	203 (48.6%)
Diffuse	139 (35.7%)	137 (32.8%)
Presence of Bacteremia		
No	381 (97.9%)	405 (97.1%)
Yes	8 (2.0%)	12 (2.8%)
Number of Baseline Pathogens		
Monomicrobial	132 (33.9%)	128 (30.9%)
Polymicrobial	256 (65.8%)	286 (69%)
Abdominal Intervention relative to randomization		
Abdominal Intervention After Randomization Abdominal Intervention Prior to Randomization	21 (5.4%) 368 (94.6%)	27 (6.4%) 390 (93.5%)

In the cIAI trial, the majority of subjects (75%) were from Eastern Europe. Subjects from the United States were 6.3% of the MITT population. The majority of the subjects were white (93.7%) and non-Hispanic or Latino (76.7%) in ethnicity. Black or African Americans comprised 0.6% of subjects. The percentage of males (57.8%) was slightly greater than females (42.2%), but balanced between the 2 treatment arms.

The following differences were noted in the MITT population: There was a higher percentage of subjects aged 65 years or older (25% versus 20%), subjects with mild to moderate renal impairment (30.8% versus 28.9%), and subjects with an APACHE II score of ≥10 (20.0% versus 16.7%) in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms respectively. In general, subjects with an infection originating from the bowel were older, had higher APACHE II scores at baseline (median scores of 7.0 for the bowel site in the ceftolozane/tazobactam plus metronidazole arm and 6.0 in the meropenem arm, and in both arms the median score for sites other than the bowel was 5.0), and were commonly renally impaired compared to subjects with an infection originating from another anatomic site.

Some degree of renal impairment at baseline was present in 30.2% of all subjects in this study, of which most were classified as mild renal impairment (25.7%). No subject was enrolled with severe renal impairment (CLCR<30 mL/min) as these subjects were excluded from the trial.

The most common diagnosis was appendiceal perforation or peri-appendiceal abscess, occurring in 378/806 (46.9%) subjects. Approximately 32% of subjects had localized complicated appendicitis (29.6% in the ceftolozane/tazobactam plus metronidazole arm and 34.1% in the meropenem arm) while nearly 15% had infection extending beyond the appendix. Diffuse peritonitis at baseline was present in 276/806 (34.2%) subjects. Infection originating from the colon and small bowel in 160/806 (19.9%) subjects, and were balanced by study arm (19.8% and 19.2%, in ceftolozane/tazobactam and meropenem arms, respectively). Overall, the incidence and distribution of intra-abdominal and blood pathogens were similar between the 2 treatment arms in the MITT and ME populations and consistent with previous studies in cIAI. The most common Gram-negative aerobes isolated at baseline from intra-abdominal specimens in the MITT population were *E. coli* (65.1%), *K. pneumoniae* (9.4%), and *P. aeruginosa* (8.9%), and the most common Gram-negative anaerobe was *Bacteroides fragilis* (13.8%). In addition, *Streptococcus spp.* were isolated in approximately 28.1% of subjects with *Streptococcus anginosus* and *Streptococcus constellatus* being the most common (7.8% and 6.1%, respectively).

Prior and Concomitant Antibacterial Agents

The protocol prohibited prior systemic antibacterial agents for IAIs for more than 24 hours prior to the first dose of study drug; unless there was a documented treatment failure with the prior antibiotic therapy received and no further doses were given post-surgery. Of a total of 32 patients who received prior antibacterial therapy within 72 hours of the study start with a duration of more than 48 hours, 14 of 16 patients in the ceftolozane/tazobactam + metronidazole treatment

arm and 14of 16 patients in the meropenem treatment arm were enrolled as failures of prior antibiotic therapy.

In the MITT population, 57.6% of the patients in both the ceftolozane/tazobactam plus metronidazole and meropenem arms received antibiotic therapy prior to study drug therapy; 5.6% of subjects were considered failures of the prior antibiotic therapy received.

Reviewer's comments: The proportion of subjects and the percentage differences are similar in the safety and MITT populations. There is an underrepresentation of African American population due to the conduct of the study in Eastern Europe. The applicant stated that difficulty to keep patients admitted in a hospital for at least the first 9 doses (approximately 3 days), as the protocol required, was the reason for not enrolling a substantial number of patients in the United States. In the safety population, 52/969 (5.3%) were from the United States. In the MITT population, 50/806 (6.2%) were from the United States. However, for this class of drug and indication, there are no known major differences in the disease course, standard of care or patient characteristics that could significantly affect its use in the US as compared with other populations. Even though overall patient characteristics in each treatment arm are comparable, small differences were noted in the MITT population, as follows: a slightly higher number of older subjects and slightly higher number of subjects with moderate renal impairment were observed in the ceftolozane/tazobactam arm. The APACHE scores at baseline were comparable, with a slightly higher proportion of APACHE scores ≥10 in the ceftolozane/tazobactam arm. A slightly higher number of subjects underwent laparotomy in the ceftolozane/tazobactam arm, which reflects the extension of the disease at baseline, evidenced as well in the slightly higher number of multiple abscesses observed in this treatment arm as compared to the comparator arm. The tables above show additional baseline characteristics of subjects in the safety and MITT populations, which show the overall comparability of the safety and the MITT populations, and the small differences noted between treatment and comparator arms in some baseline characteristics of the MITT population, as summarized above. The use of prior antibacterial treatments was balanced between arms.

6.1.3 Subject Disposition

A total of 993 patients were randomized into the study; 487 patients were randomized to the ceftolozane/tazobactam plus metronidazole treatment arm and 506 patients were randomized to the meropenem treatment arm. The majority of patients (73.5%) were enrolled in Eastern Europe. A high percentage of patients in both treatment arms completed the study (92.8% versus 94.1% in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms, respectively).

Table 13: Disposition of Subjects - MITT Population - Reviewer's table –

Number of Subjects*:	**Ceftolozane/ Tazobactam + Metronidazole (N=389)** n (%)	**Meropenem (N=417)** n (%)	**Total (N=806)** n (%)
Receiving Study Drug	388 (99.7)	414 (99.3)	802 (99.5)
Completing Study	363 (93.3)	398 (95.4)	761 (94.4)
Completing Study Drug	361 (92.8)	390 (93.5)	751 (93.2)
Prematurely Withdrawing from Study	26 (6.7)	19 (4.6)	45 (5.6)
Prematurely Discontinuing Study Drug	27 (6.9)	24 (5.8)	51 (6.3)
Primary Reason for Premature Withdrawal from Study			
Adverse Event[1]	11 (2.8)	7 (1.7)	18 (2.2)
Lack of Efficacy	0	2 (0.5)	2 (0.2)
Major Protocol Violation	0	1 (0.2)	1 (0.1)
Patient's Decision	8 (2.1)	5 (1.2)	13 (1.6)
Lost to Follow-Up	7 (1.8)	3 (0.7)	10 (1.2)
Other	0	1 (0.2)	1 (0.1)
Primary Reason for Premature Discontinuation of Study Drug			
Adverse Event[2]	12 (3.1)	11 (2.6)	23 (2.9)
Lack of Efficacy	4 (1.0)	3 (0.7)	7 (0.9)
Major Protocol Violation	1 (0.3)	0 (0.1)	1 (0.3)
Patient's Decision	9 (2.3)	6 (1.4)	15 (1.9)
Other	1 (0.3)	4 (1.0)	5 (0.6)

*: Patients may be counted in more than one category
1 11/11 (100%) of ceftolozane/tazobactam plus metronidazole and 6/7 (86%) of meropenem patients had adverse events with an outcome of death.
[2] 6/12 (50%) of ceftolozane/tazobactam plus metronidazole and 3/11 (27%) of meropenem patients had adverse events with an outcome of death.
Source: Adapted from Statistical Reviewer Table

Table 14: Disposition of Subjects – Safety Population

Disposition Summary - Ceftolozane And Tazobactam NDA206829 / cxa-ciai-10-08-10-09 ActArm

9 rows

	Treatment (N=482)		Comparator (N=497)		Total (N=979)	
Disposition	**#**	**%**	**#**	**%**	**#**	**%**
<Multiple Dispositions>	2	0.4%	0	0%	2	0.2%
ADVERSE EVENT	13	2.7%	7	1.4%	20	2%
COMPLETED	453	94%	477	96%	930	95%
LACK OF EFFICACY	0	0%	2	0.4%	2	0.2%
LAST TELEPHONE ATTEMPT	2	0.4%	4	0.8%	6	0.6%
LOST TO FOLLOW-UP	2	0.4%	1	0.2%	3	0.3%
MAJOR PROTOCOL VIOLATION	0	0%	1	0.2%	1	0.1%
PROTOCOL VIOLATION	1	0.2%	0	0%	1	0.1%
WITHDRAWAL BY SUBJECT	9	1.9%	5	1%	14	1.4%

Source: Reviewer's table using tabulation data: Demographic dataset, with Empirica Study

Medical Reviewer comment: A high percentage of patients, similarly high in both treatment and comparator arms, completed the study. The disposition events were similar across the safety and MITT populations. There were more patients in the ceftolozane/tazobactam plus metronidazole than in the meropenem arm who withdrew from the study [26/389 (6.7%) vs. 19/417 (4.6%)] and who prematurely discontinued study drug [27/389 (6.9%) vs. 24/417 (5.8%)].

Table 15: Populations and Reasons for Exclusion from Populations (Safety, MITT, CE, Expanded ME, ME, and CE Populations)

Population **Reason for Exclusion**	**Ceftolozane/ Tazobactam + Metronidazole (N=487) n (%)**	**Meropenem (N=506) n (%)**	**Total (N=993) n (%)**
Safety Population	482	497	979
Excluded from the Safety Population	5 (1.0)	9 (1.8)	14 (1.4)
MITT Population	389 (79.9)	417 (82.4)	806 (81.2)

Not MITT Evaluable	98 (20.1)	89 (17.6)	187 (18.8)
Did not have Baseline Infecting Pathogen	90 (18.5)	78 (15.4)	168 (16.9)
Subjects from closed sites[a]	11 (2.3)	12 (2.4)	23 (2.3)
CE Population at TOC	375 (77.0)	399 (78.9)	774 (77.9)
Not CE Evaluable	112 (23.0)	107 (21.1)	219 (22.1)
Did not meet minimal disease criteria[b]	6 (1.2)	6 (1.2)	12 (1.2)
Did not meet key inclusion criteria or met any key exclusion criteria[c]	17 (3.5)	16 (3.2)	33 (3.3)
Received active, confounding non-study antibiotic[d]	24 (4.9)	24 (4.7)	48 (4.8)
Received incorrect study drug	1 (0.2)	1 (0.2)	2 (0.2)
Inadequate duration of study drug therapy[e]	16 (3.3)	14 (2.8)	30 (3.0)
Not compliant with study drug treatment	4 (0.8)	3 (0.6)	7 (0.7)
Indeterminate clinical response assessment at TOC	57 (11.7)	46 (9.1)	103 (10.4)
TOC clinical response assessment out of window[f]	19 (3.9)	25 (4.9)	44 (4.4)
Potential unblinding	2 (0.4)	2 (0.4)	4 (0.4)
Inadequate infection source control[g]	13 (2.7)	12 (2.4)	25 (2.5)
Subjects from closed sites[a]	11 (2.3)	12 (2.4)	23 (2.3)
CE at LFU Population[h]	350 (71.9)	374 (73.9)	724 (72.9)
Not CE at LFU Evaluable	137 (28.1)	132 (26.1)	269 (27.1)
Expanded ME Population	307 (63.0)	345 (68.2)	652 (65.7)
Not Expanded ME Evaluable	180 (37.0)	161 (31.8)	341 (34.3)
Did not meet MITT Criteria	98 (20.1)	89 (17.6)	187 (18.8)
Did not meet CE Criteria	112 (23.0)	107 (21.1)	219 (22.1)
ME Population	275 (56.5)	321 (63.4)	596 (60)
Not ME Evaluable	212 (43.5)	185 (36.6)	397 (40)
Did not meet MITT Criteria	**98 (20.1)**	**89 (17.6)**	**187 (18.8)**
Did not meet CE Criteria	**112 (23.0)**	**107 (21.1)**	**219 (22.1)**
Did not have susceptible Baseline Infecting Pathogen	**50 (10.3)**	**38 (7.5)**	**88 (8.9)**
ME at LFU[i]	**258 (53.0)**	**304 (60.1)**	**562 (56.6)**
Not ME at LFU Evaluable	**229 (47.0)**	**202 (39.9)**	**431 (43.4)**

CE = Clinically Evaluable; LFU = Last follow-up; ME = Microbiologically Evaluable; MITT = Microbiological Intent-to-treat. N=Number of subjects in Intent-to-treat population. n=Number of subjects in specific category; TOC=Test of cure. The actual treatment for Subject 1008-6103-001 is missing so planned treatment (meropenem) is used for this subject.
Two subjects received wrong drug (Subject Nos. 1008-6104-001 and 1008-4020-001). Notes: Percentages are calculated as 100 x (n/N). Subjects may be excluded from a population for more than one reason.
[a:] Two sites (Sites 1008-4024 and Site 1009-4227) were closed due data integrity concerns and data from these sites were excluded in from the primary efficacy analysis in the MITT population and efficacy analyses in the evaluable populations (CE, ME and Expanded ME);
[b]: Minimal disease criteria are defined as meeting inclusion criteria (1, 5, 6, 10) and not meeting exclusion criteria (1, 2, 3, 4, 5).
[C]: Key inclusion criterion (8), and Key exclusion criteria (6, 7, 8).
[D]: Subjects who were assessed as a clinical failure prior to or at the TOC visit were not excluded from the [C]E population, if they received active nonstudy antibiotic therapy.
[E]: Duration of study therapy is between 3 to 11 days or up to 15 days if extension criterion is met.
[F]: Defined as occurring 24 to 32 days after first administration of study drug.
[G]: As determined by independent blinded review performed by surgical review panel.
[H]: Only CE subjects that were cured at the TOC Visit were eligible for the CE at LFU population.
[I:] Only ME subjects that were cured at the TOC Visit were eligible for the ME at LFU population.
Source: Table 14.1.1.2.3 CSR

A total of 14 subjects were excluded from the safety population because they were randomized but not dosed (5 subjects in the ceftolozane/tazobactam plus metronidazole treatment arm and 9 subjects in the meropenem treatment arm). Two subjects were included in specific populations per the statistical analysis plan as follows: subject 1008-4020-001 mistakenly received meropenem for the duration of therapy and is included in the meropenem treatment arm for all safety analyses, but included in the ceftolozane/tazobactam plus metronidazole treatment arm for all efficacy analyses (as randomized); Subject 1008-6104-001 was randomized to meropenem, but received a single dose of ceftolozane/tazobactam plus metronidazole and was included in the ceftolozane/tazobactam plus metronidazole treatment arm for all safety analyses and meropenem treatment arm for all efficacy analyses. The percentage of subjects included in the MITT population and the reasons for exclusion were balanced between treatment arms. The MITT population included a total of 806 (81.2%) who had a qualifying baseline pathogen, and the percentage of subjects from each treatment arm was comparable (79.9% versus 82.4% in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms, respectively). Exclusion from the MITT population was due to the lack of a qualifying baseline pathogen (16.9%). In addition, following a Sponsor commissioned audit, 2 sites (Site 1008-4024 and Site 1009-4227) were closed due to data integrity concerns, and the subjects enrolled at these sites (N=23) were excluded from all efficacy populations, including the MITT population.
The ME population consisted of 596 (60.0%) subjects (including 275 [56.5%] versus 321 [63.4%] subjects in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms, respectively). The imbalance in the size of the ME population between treatment arms was due to the difference in the number of subjects without a baseline-infecting pathogen, the number of subjects with a non-susceptible baseline pathogen, and the number of subjects with a missing or indeterminate clinical response assessment at the TOC visit, all of which were higher in the ceftolozane/tazobactam plus metronidazole arm. The majority of baseline pathogens non-

susceptible to ceftolozane/tazobactam were pathogens intrinsically resistant to ceftolozane/tazobactam including *Enterococcus* spp. and *Staphylococcus* spp.

Medical Reviewer's comment: *The number and reasons for exclusions were balanced by treatment arm, except for the number of indeterminate outcomes which were greater in the ceftolozane/tazobactam plus metronidazole arm. However, because indeterminate outcomes were not counted as cures, the differences did not affect the overall assessment of primary efficacy endpoint. The ME population (population of the key secondary endpoint) was smaller in the ceftolozane/tazobactam arm also due to the missing or indeterminate outcomes. Please see the table of reasons for indeterminate outcomes and comment above. The majority of the missing and indeterminate outcomes are not due to random events; they are mainly due to adverse events and deaths that occurred prior to the TOC visit.*

Protocol Violations

Overall, 63/993 (6.3%) of patients enrolled violated an inclusion criterion or an exclusion criterion. The most common inclusion/exclusion criterion violated was exclusion criterion number 6 (use of systemic antibiotic therapy for IAI for more than 24 hours prior to the first dose of study drug); 12 subjects in the ceftolozane/tazobactam plus metronidazole treatment arm and 9 in the meropenem treatment arm violated this criterion. Violations of other inclusion or exclusion criteria were similar between treatment groups. There were 598 (60.0%) patients in the ITT population who had a protocol deviation during the study. The incidence and types of protocol deviations were similar between treatment arms.

The majority of protocol deviations did not lead to exclusion of patient data from analysis. The most frequently reported deviations during the study were related to the timing or collection of study assessments and were balanced across treatment arms.

Ninety-six (9.7%) patients were randomized within the wrong primary site of infection strata. The majority of the mis-stratified patients had appendix as their primary site of infection but were stratified to bowel based on anatomic location despite the protocol-defined stratification criteria.

During the conduct of the trial, 2 sites (Site 1009-4227 and Site 1008-4024) were closed due to concerns with GCP noncompliance and potential risk to data integrity.

- 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, 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.

Of note, 23 patients from 2 study sites (Site 1009-4227 and Site 1008-4024) were excluded from MITT, CE, and ME efficacy analyses due to concerns regarding data. These patients, however, were included in the safety population for analysis.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the clinical cure rate in the MITT population at the TOC visit, and this outcome relied on the investigator-based assessment of clinical response. These assessments were made at both the EOT and TOC visits.
The following analysis populations were defined to assess primary and secondary endpoints.

Primary Endpoint

The primary endpoint was the clinical cure rate at the TOC visit in the primary MITT population.

In the analysis of clinical response for the primary efficacy outcome measure, ceftolozane/tazobactam plus metronidazole met the statistical criteria for non-inferiority to meropenem at the TOC visit in the MITT population (i.e., the lower bound of the 2-sided 95% CI for the difference in cure rates was greater than -10%).
Missing or indeterminate outcomes had the same effect on outcome as failures did in the MITT population, but excluded in the per-protocol populations (ME, CE, and Expanded ME).

Table 16: Clinical Response at the Test-of-Cure in the MITT population

MITT	Ceftolozane/tazobactam + Metronidazole, n (%)	Meropenem n (%)	% Difference (95% CI)
	N=389	N=417	
Cure	323 (83.0)	365 (87.3)	Applicant: -4.2 (-8.9, 0.5)[1] Reviewer: -4.6 (-9.4, 0.1)[2] -4.3 (-9.2, 0.7)[3]
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	

1 Newcombe CI with Minimum Risk Weights stratified by region & primary site of infection on eCRF
2 Newcombe CI w/ Minimum Risk Weights stratified by region & randomized primary site of infection
3 Unstratified Newcombe CI

Medical Reviewer's comment: Minor differences were found between the Applicant's analysis and the reviewer's, as indicated in the table; however, these did not affect the overall conclusion of efficacy. Ceftolozane/tazobactam plus metronidazole met the non-inferiority margin for the primary efficacy endpoint.

The treatment difference in the MITT population (primary outcome) as shown in the table above, was mainly driven by an imbalance in missing or indeterminate clinical response assessments between the treatment arms. The table below shows the reasons for the outcome of indeterminate in both treatment arms.

Table 17: Subjects with an Outcome of Indeterminate at the TOC visit

Reasons	Tolo/Taz +Mtz (N=389)	Meropenem (N=417)	Total (N=806)
Patients with Indeterminate clinical response at TOC	34 (8.7%)	19 (4.6%)	53 (6.6%)
Cure at EOT & LFU, no TOC visit	5 (1.3)	1 (0.2)	6 (0.7)
Cure at EOT, discontinued study	5 (1.3)	5 (1.2)	10 (1.2)
AE	1 (0.3)	3 (0.7)	4 (0.5)
Subject Withdrawal	1 (0.3)	1 (0.2)	2 (0.2)
Lost to Follow-up	3 (0.8)	1 (0.2)	4 (0.5)
Prematurely discontinued study drug	21 (5.4)	11 (2.6)	32 (4.0)
Adverse Events	10 (2.6)	4 (1.0)	14 (1.7)
Protocol Violation	1 (0.3)	0	1 (0.1)
Subject Withdrawal	9 (2.3)	5 (1.2)	14 (1.7)
Other	1 (0.3)	2 (0.5)	3 (0.4)
Death prior to TOC	7 (1.8)	5 (1.2)	12 (1.5)
Randomized, not treated	1 (0.3)	3 (0.7)	4 (0.5)

Note: Subjects have been counted in more than one category if they have met criteria for more than one category.
Source: adapted from Table 20 from the CSR

Medical Officer comment: There was a higher number of indeterminate outcomes in the ceftolozane/tazobactam plus metronidazole arm than in the meropenem arm. This difference appears to be driven by a greater number of premature discontinuations in the ceftolozane-tazobactam arm that were primarily due to adverse events and withdrawals prior to the TOC visit in the ceftolozane/tazobactam plus metronidazole arm. Most of the adverse events causing withdrawals were fatal and represent complications of the underlying infection and co-morbidities and a potential lack of efficacy of the treatment. The deaths and AEs causing withdrawals are counted in this table more than once (under "Prematurely discontinued study drug," "AE" and "Death prior to TOC").

Prior and concomitant systemic antibacterial agents
The distribution of the antibacterial treatments given within 72 hours of study drug start, by duration and by relation to the time of the surgical procedure (before or after) were comparable in both treatment arms and are shown in the table below.

Table 18: Summary of Patients with Prior Antibiotic Therapy before and after the First Intra-abdominal Procedure within 72 hours of start of study drug (MITT Population)

	Ceftolozane/Tazobactam + Metronidazole (N=389)			**Meropenem (N=417)**			**Overall (N=806)**		
Category	**<=24h n (%)**	**>24 to 48h n (%)**	**>48h * n (%)**	**<=24h n (%)**	**>24 to 48h n (%)**	**>48h * n (%)**	**<=24h n (%)**	**>24 to 48h n (%)**	**>48h * n (%)**
Initiated Before Procedure									
Overall	155 (39.8)	5 (1.3)	16 (4.1)	178 (42.7)	6 (1.4)	16 (3.8)	333 (41.3)	11 (1.4)	32 (4.0)
Single Dose	105 (27.0)	0 (0.0)	0 (0.0)	120 (28.8)	0 (0.0)	0 (0.0)	225 (27.9)	0 (0.0)	0 (0.0)
Multiple Doses	50 (12.9)	5 (1.3)	16 (4.1)	58 (13.9)	6 (1.4)	16 (3.8)	108 (13.4)	11 (1.4)	32 (4.0)
Initiated After Procedure									
Overall	38 (9.8)	0 (0.0)	0 (0.0)	32 (7.7)	0 (0.0)	0 (0.0)	70 (8.7)	0 (0.0)	0 (0.0)
Single Dose	34 (8.7)	0 (0.0)	0 (0.0)	22 (5.3)	0 (0.0)	0 (0.0)	56 (6.9)	0 (0.0)	0 (0.0)
Multiple Doses	4 (1.0)	0 (0.0)	0 (0.0)	10 (2.4)	0 (0.0)	0 (0.0)	14 (1.7)	0 (0.0)	0 (0.0)

Notes: N=number of patients in the specified treatment arm in MITT population. n=number of patients in the specified category. Percentages are calculated as n/N x 100.
Duration of prior antibiotic therapy (<=24, >24 to 48, >48, in hours) is calculated as the time window from the start to the end of the prior antibiotic therapy. If a patient got multiple doses of prior antibiotic therapy, the duration is calculated from the start of the first dose to the end of the last dose. Patients who received prior antibiotic therapy within 72 hours before the start of study drug are summarized.
6 patients are not present due to insufficient information about type of dosing (single dose vs. multiple doses) or duration.
* 14/16 of the patients with >48h prior antibiotic therapy in the ceftolozane/tazobactam + metronidazole treatment arm, 14/16 of the patients in the meropenem treatment arm and 28/32 of the patients overall were enrolled as failures of prior antibiotic therapy. Source: Applicant's response to information request.

The most common prior antibiotics administered were imidazole derivatives (28.5% versus 25.9% in the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively) and third-generation cephalosporins (19.8% versus 16.1% in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms, respectively). The use of concomitant non-study antibacterial medications in the MITT population prior to the TOC visit was balanced between treatment arms (14.9% versus 12.9% of subjects in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms, respectively) was reported mainly in subjects who failed study therapy or required treatment for a distant site infection other than cIAI.

Of the 22 patients who received non-study antibiotics for a non intra-abdominal infection in the MITT population, 5 of 10 patients in the ceftolozane/tazobactam plus metronidazole arm and 9 of 12 patients in the meropenem arm were assessed as clinical cure at the TOC visit by the investigator. The applicant performed an analysis of cure rates with and without prior antibacterial therapy before and after the surgical procedure, per our request. The results are shown in the table below and reflect comparability of study arms with lower cure rates with use of prior antibacterial agents.

Table 19: Clinical Cure Rate at TOC Visit by Prior Antibacterial Therapy (MITT Population)

		Ceftolozane/ Tazobactam + Metronidazole (N=389)	**Meropenem (N=417)**	**Overall (N=806)**	**% Difference (95% CI)**
Prior antibiotics	N1	218	234	452	-4.4
Clinical cure	n (%)	173 (79.4)	196 (83.8)	369 (81.6)	(-11.6, 2.7)
95% CI for percentage cure rate		(73.5, 84.2)	(78.5, 87.9)	(77.8, 84.9)	
Before procedure	N1	179	201	380	-3.7
Clinical cure	n (%)	143 (79.9)	168 (83.6)	311 (81.8)	(-11.6, 4.1)
95% CI for percentage cure rate		(73.4, 85.1)	(77.8, 88.1)	(77.7, 85.4)	
After procedure	N1	38	32	70	-11.2
Clinical cure	n (%)	29 (76.3)	28 (87.5)	57 (81.4)	(-28.4, 7.7)
95% CI for percentage cure rate		(60.8, 87.0)	(71.9, 95.0)	(70.8, 88.8)	
No Prior antibiotics	N1	171	183	354	-4.1

Clinical cure	n (%)	150 (87.7)	168 (91.8)	318 (89.8)	(-10.7, 2.3)
95% CI for percentage cure rate		(82.0, 91.8)	(86.9, 95.0)		

Notes: N=number of patients in the specified treatment arm in MITT population. N1=number of patients in the specified category. n=number of patients who were clinical cure in the specified category. Percentages are calculated as n/N1 x 100. The 95% Wilson Score confidence intervals (CIs) are used for percentage cure rate in each treatment arm and treatment difference.
Patients who received prior antibiotic therapy within 72 hours before the start of study drug are summarized. **Source:** Table 2 of 1.11.3 Efficacy information amendment (applicant's response to clinical information request)

Patients Needing a Second Surgery after 72 Hours of Enrollment to Control Infection

According to the protocol, any patient who had a surgical procedure or drainage with the purpose of controlling the intra-abdominal infection after 72 hours of starting study drug would be considered a clinical failure. The applicant submitted listings of patients with additional procedures, but the reasons for the procedures performed after 72 hours were not consistently collected. Overall, 57/806 (7.1%) patients in the MITT population had a second surgery after 72 hours, with a similar proportion of patients in each treatment arm. The majority of these patients were assessed as clinical failures by the investigator. Of patients with an investigator determined outcome of cure in the MITT population, 8 patients in the ceftolozane/tazobactam plus metronidazole arm and 15 in the meropenem arm had a second procedure. The majority of these procedures were planned procedures that did not represent an operative intervention (e.g., removal of the drain).

Medical Reviewer comment: The protocol violations, including those related to the use of prior and concomitant antibacterial therapy when it was not allowed by the protocol, did not significantly affect the efficacy conclusions. In both arms the cure rates were lower with prior use of antibacterial therapy, suggesting that this treatment did not introduce a bias in favor of the study drug efficacy. Although the reason for the need of a second surgical procedure after 72 hours of start of the study drug was not uniformly collected, the number of procedures performed after 72 hours of study drug start per treatment arm was recorded. The number of patients with a second procedure and an outcome of cure was greater in the meropenem arm than in the ceftolozane/tazobactam plus metronidazole arm (15 patients in the meropenem arm and 8 patients in the ceftolozane/tazobactam plus metronidazole arm). This provides reassurance that procedures performed to control the intra-abdominal infection after 72 hours of initiation of study drug did not bias the overall efficacy conclusions in favor of the study drug.

Per Patient Clinical Cure Rates by Baseline Pathogen

The tables below show the clinical cure rates per pathogen in the MITT and in the ME Populations. For more details about microbiological sensitivity and outcomes, please refer to the review by Dr. Kerian Grande Roche, Ph.D., the Microbiology Reviewer.

Table 20: Per Patient Clinical Cure Rates at TOC (MITT Population)

Organism Group **Pathogen**	**ZERBAXA plus metronidazole** **n/N (%)**	**Meropenem** **n/N (%)**
Aerobic Gram-negative	263/313 (84.0)	303/346 (87.6)
Escherichia coli	216/255 (84.7)	238/270 (88.2)
Klebsiella pneumoniae	31/41 (75.6)	27/35 (77.1)
Pseudomonas aeruginosa	30/38 (79.0)	30/34 (88.2)
Enterobacter cloacae	21/26 (80.8)	24/25 (96.0)
Klebsiella oxytoca	14/16 (87.5)	24/25 (96.0)
Proteus mirabilis	11/12 (91.7)	9/10 (90.0)
Aerobic Gram-positive	176/222 (79.3)	195/222 (87.8)
Streptococcus anginosus	26/36 (72.2)	24/27 (88.9)
Streptococcus constellatus	18/24 (75.0)	20/25 (80.0)
Streptococcus salivarius	9/11 (81.8)	9/11 (81.8)
Anaerobic Gram-negative	112/137 (81.8)	141/154 (91.6)
Bacteroides fragilis	42/47 (89.4)	59/64 (92.2)
Bacteroides ovatus	38/45 (84.4)	44/46 (95.7)
Bacteroides thetaiotaomicron	21/25 (84.0)	40/46 (87.0)
Bacteroides vulgatus	12/15 (80.0)	24/26 (92.3)

Table 21: Per Patient Clinical Cure Rates at TOC by Baseline Pathogen (ME Population)

Organism Group **Pathogen**	**Ceftolozane/ Tazobactam + Metronidazole** **n/N (%)**	**Meropenem** **n/N (%)**
Aerobic Gram-negative	230/243 (94.7)	266/282 (94.3)
Escherichia coli	190/201 (94.5)	211/225 (93.8)
Klebsiella pneumoniae	27/28 (96.4)	22/25 (88.0)
Pseudomonas aeruginosa	25/25 (100)	27/28 (96.4)
Enterobacter cloacae	18/21 (85.7)	22/22 (100)
Klebsiella oxytoca	12/12 (100)	21/22 (95.5)
Proteus mirabilis	10/11 (90.9)	9/10 (90.0)
Aerobic Gram-positive	128/141 (90.8)	155/167 (92.8)
Streptococcus anginosus	25/30 (83.3)	23/23 (100)
Streptococcus constellatus	17/18 (94.4)	20/23 (87.0)
Streptococcus salivarius	9/10 (90.0)	8/8 (100)
Anaerobic Gram-negative	104/109 (95.4)	132/137 (96.4)
Bacteroides fragilis	39/41 (95.1)	56/57 (98.3)
Bacteroides ovatus	36/37 (97.3)	42/42 (100)

Organism Group Pathogen	**Ceftolozane/ Tazobactam + Metronidazole n/N (%)**	**Meropenem n/N (%)**
Bacteroides thetaiotaomicron	20/20 (100)	40/43 (93.0)
Bacteroides vulgatus	12/13 (92.3)	21/22 (95.5)

The clinical cure rates for polymicrobial and monomicrobial infections were also explored and are shown in the table below.

Table 22: Summary of Clinical Cure Rates for Polymicrobial and Monomicrobial Infections (MITT Population)

No. of Pathogens	**MITT - N (%)[a]**		
	Ceftolozane/ Tazobactam + Metronidazole	**Meropenem**	**Percentage Difference (95% CI)[b]**
Polymicrobial	209/257 (81.3)	255/288 (88.5)	-7.2 (-13.33, -1.22)
Monomicrobial	114/132 (86.4)	109/129 (84.5)	1.9 (-6.79, 10.57)

MITT = Microbiological Intent-to-Treat. ME = Microbiologically evaluable. Notes: n=Number of subjects in specific category. N=Number of subjects in MITT population within the subgroup.
[a]: Percentages are calculated as 100 x (n/N1), percentage of subjects in MITT population.
[b]: 95% confidence intervals (CIs) are calculated as Wilson Score CIs. Source: Table 14.2.2.2.31 and Table 14.2.2.2.32.

Medical Reviewer's comment: These results support the efficacy of ceftolozane/tazobactam plus metronidazole in the treatment of patients with the documented pathogens listed. Overall, similar clinical cure rates were observed in both treatment arms for all Enterobacteriaceae. Lower clinical cure rates were observed for Streptococcus anginosus and Streptococcus constellatus in the ceftolozane/tazobactam plus metronidazole arm in the MITT population. The clinical evaluation of the activity of ceftolozane/tazobactam against anaerobes is limited by the concomitant use of metronidazole in the trial. In the subgroup of polymicrobial infections, a lower efficacy (percentage difference of -7.2 in the clinical cure rate) was observed for ceftolozane/tazobactam plus metronidazole compared with meropenem.

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary efficacy variable was clinical cure rate at the TOC visit in the ME population. In the ME population, clinical cure rates were higher in both treatment arms compared with the MITT population. The weighted difference in clinical cure rates ([ceftolozane/tazobactam plus metronidazole] minus meropenem) was -1.0% with a 2-sided 95% CI of -4.52% to 2.59%, supportive of the non-inferiority of ceftolozane/tazobactam plus metronidazole versus meropenem.

Table 22: Key Secondary Endpoint

Secondary Analysis		**Ceftolozane/tazobactam plus metronidazole** N=275	**Meropenem** N=321	
ME Population	Cure	259 (94.2)	304 (94.7)	-1.0 (-4.52, 2.59)
	Failure	16 (5.8)	17 (5.3)	

Using a data-as-observed approach, the analysis is stratified by region and primary site of infection as recorded on the eCRF. Note: Patients from Site 1008-4024 and Site 1009-4227 are excluded from the analysis. Source: Table 14.2.2.1.1 from CSR

Surgical Review Panel

- All patients in the MITT population with an outcome of failure or those with an outcome of cure and a second procedure were reviewed by the Surgical Review Panel prior to database lock with the exception of one patient (Subject No. 1009-4511-001) who was considered a failure due to a post-surgical wound infection.
- The Surgical Review Panel (SRP) re-classified several patients after reviewing surgical procedures to determine adequacy of source control. However, these re-classifications did not override investigator assessments in the primary analysis. The re-classifications affected the CE and ME populations only.
  - The SRP reviewed 73 patients (35 patients from the ceftolozane/tazobactam plus metronidazole arm and 38 patients from the meropenem arm), which included 64 failures (31 in the ceftolozane/tazobactam plus metronidazole arm and 33 in the meropenem arm) and 9 cures (4 ceftolozane/tazobactam plus metronidazole, 5 meropenem) with a second intra-abdominal procedure.
  - Twenty-four patients (12 [2.4%] versus 12 [2.4%] subjects in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms, respectively) were considered nonevaluable by the SRP due to inadequate source control and were excluded from the CE and ME populations; because the distribution of nonevaluable patients was similar across treatment arms, there was no meaningful impact on the treatment differences in efficacy analyses.

- 2 patients (1 per treatment arm) were changed from cure to failure due to evidence of an ongoing infection
- 4 patients (1 ceftolozane/tazobactam + metronidazole, 3 meropenem) were changed from cure to indeterminate due to inadequate source control

Primary analysis (unstratified) with the SRP re-classifications showed a treatment difference of -3.8% (-8.9, 1.2).

6.1.6 Other Endpoints

Other secondary efficacy variables included:

- Clinical cure rate at the TOC visit in the CE Population.

Clinical cure rates were comparably higher in the CE than in the MITT population and similar between the 2 treatment arms. A total of 353 of 375 (94.1%) and 375 of 399 (94.0%) patients in the CE population for the ceftolozane/tazobactam plus metronidazole and meropenem arms, respectively, were clinical cures.

- Per-subject microbiological success rates at the TOC visit.

The applicant determined an overall microbiological response for each subject based on individual microbiological responses for each baseline pathogen at both the EOT and TOC visits. In order for the patient to have a favorable overall microbiological response (i.e., success), each baseline pathogen must have had a favorable microbiological outcome. If the outcome for any pathogen was unfavorable, the subject was considered an overall microbiological failure.
The per-patient microbiological success rates were similar in both arms in the MITT population: 332 of 389 patients (85.3%) in the ceftolozane/tazobactam plus metronidazole arm and 370 of 417 patients (88.7%) in the meropenem arm and ME population: 264 of 275 patients (96%) in the ceftolozane/tazobactam plus metronidazole arm and 307 of 321 patients (95.6%) in the meropenem arm, with higher rates in the ME population in both arms.

- Per-pathogen microbiological response rates at the TOC visit

The applicant determined a microbiological response for each pathogen isolated at baseline at both the EOT and TOC visits. Microbiological response categories were eradication, presumed eradication, persistence, persistence acquiring resistance, presumed persistence, and indeterminate. Favorable microbiological responses included “eradication” or “presumed eradication.” Unfavorable responses were considered “persistence,” “persistence acquiring resistance,” and “presumed persistence.”

Ceftolozane/tazobactam plus metronidazole demonstrated per-pathogen microbiological success rates comparable to meropenem in the ME population among patients with common Gram

negative aerobic pathogens including *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *E. cloacae*, *K. oxytoca*, and *P. mirabilis*; Gram-positive aerobic pathogens such as *S. anginosus, S. constellatus*, and *S. salivarius*; and Gram-negative anaerobes such as *B. fragilis, B. ovatus, B. thetaiotaomicron*, and *B. vulgatus*. For Gram-negative aerobic pathogens, microbiological eradication rates in the ME population of 234/243 (96.3%) and 269/282 (95.4%) were seen in the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively. The microbiological eradication rates for the 2 most common Enterobacteriaceae, were 193/201 (96.0%) versus 214/225 (95.1%) for *E. coli* and 28/28 (100%) versus 22/25 (88.0%) for *K. pneumoniae* for the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively. Against *P. aeruginosa*, the microbiological eradication rates for ceftolozane/tazobactam plus metronidazole and meropenem were 25/25 (100%) and 28/28 (100%), respectively.
Ceftolozane/tazobactam demonstrated activity comparable to meropenem against ESBL-producing Enterobacteriaceae. Clinical cure rates in the ME population were 100% (22/22) and 88.5% (23/26) for the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively.

- Proportion of subjects with superinfections or new infections.

Superinfections and new infections were uncommon and mostly due to organisms intrinsically resistant to ceftolozane/tazobactam (*Enterococcus* spp.). Superinfections were seen in 2.6% and 3.1% of subjects in the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively, in the MITT population. Likewise, 3.1% and 2.2% of subjects in the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively, had new infections. The majority of these were also due to *Enterococcus spp*., followed by Gram negative organisms (*Escherichia coli and Klebsiella spp.*) and *Staphylococcus spp*. The proportion, frequency and type of organisms were comparable in both treatment arms.
There were no patients with susceptible baseline pathogens that became resistant to meropenem, and likewise, there were no patients with susceptible pathogens that became resistant to ceftolozane/tazobactam.

- Clinical cure rate at the EOT and LFU visits.

Cure rates at the EOT in the MITT population were higher than at the TOC visit in both treatment arms. A total of 347 of 389 subjects (89.2%) and 385 of 417 subjects (92.3%) were cures at EOT. Clinical cures at LFU (sustained clinical cures) were lower than at EOT and TOC in both arms and comparable between arms. A total of 321 of 389 subjects (82.5%) in the ceftolozane/tazobactam plus metronidazole arm and 361 of 417 subjects (86.6%) in the meropenem arm were cures at LFU.

- Clinical cure rate at the TOC visit for subjects infected with an ESBL-producing organism at baseline.

Overall, a total of 58 subjects in the MITT population had baseline intra-abdominal pathogens that were confirmed to be ESBL-positive, including 29 subjects in each arm (7.5% versus 7.0% of subjects in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms,

respectively). Of the 58 subjects with ESBL-positive pathogens, clinical cure rates were 25/29 (86.2%) versus 24/29 (82.8%) subjects in the ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms, respectively.

• Per-pathogen microbiological response rate at the TOC visit in subjects infected with an ESBL-producing organism at baseline.
The Applicant did not present these data.

• Per-pathogen clinical cure rate at the TOC visit by baseline minimum inhibitory concentration (MIC).
There was insufficient data to draw any conclusions about trends in outcome by ceftolozane/tazobactam MIC for Gram-negative aerobic organisms. Outcomes by MIC for anaerobes were summarized, but the MIC values to ceftolozane/tazobactam may not have been relevant as the majority were susceptible to metronidazole.

6.1.7 Subpopulations

The applicant presented outcomes by subgroups for the following characteristics: site of infection, number of abscesses, age, sex, APACHE scores, baseline creatinine levels, prior use of antibacterial therapy, geographical region and type of procedure. Some differences in clinical cure rates in favor of meropenem in the MITT population were observed in the following subgroups: subjects with colon as their anatomic site of infection; an APACHE II score ≥10; baseline moderate renal impairment (CLCR <50 mL/min); and age ≥65 to <75 years. There was also a higher number of patients with a missing or indeterminate clinical response assessment in these subgroups in the ceftolozane/tazobactam plus metronidazole arm.

Cure Rates by Baseline Characteristics
The table below presents cure rates by baseline characteristics of the MITT population. Some patients may be counted in more than one category, for example, most patients older than 65 years also had APACHE scores >10 and creatinine clearance <80 mL/min and bowel as the site of primary infection.

Table 23: Cures at TOC Visit in MITT population by baseline characteristics- cIAI (Medical Reviewer's table using JMP ADSL and ADXO datasets)

Cure Outcomes by Subgroups	**Ceftolozane/tazobactam (n/total) (%)**	**Meropenem (n/total) (%)**
Total Cures	323/389 (83%)	364/417 (87%)
Females	142/171 (83%)	147/169 (86%)
Males	181/218 (83%)	217/248 (87%)
Age >=18 and <65	254/289 (87%)	294/332 (88%)
Age >=65 and <75	37/54 (68%)	43/48 (89%)
Age >75	32/46 (69%)	27/37 (72%)
Bowel site	53/77 (68%)	63/80 (78%)
Other Site	270/309 (87%)	301/336 (89%)

White Race	306/367 (83%)	344/388 (88%)
Other Races	17/22 (77%)	20/28 (71%)
APACHE score <10 APACHE score >10	268/310 (86%) 54/78 (69%)	308/347 (88%) 56/70 (80%)
Creatinine Clearance>=30 to <50 mL/min Creatinine Clearance >=50 to <80 mL/min Creatinine Clearance >80 mL/min	11/23 (47%) 80/98 (81%) 232/268 (86%)	9/13 (69%) 93/109 (85%) 262/295 (88%)
Eastern Europe	256/297 (86%)	281/308 (91%)
North America	17/26 (65%)	19/25 (76%)
Rest of the World	11/19 (57%)	13/20 (65%)
South America	34/36 (94%)	41/45 (91%)
Western Europe	5/11 (45%)	10/19 (52%)

Medical Reviewer comments*: In the subgroup categories, there were lower cure rates in the patients ≥65 years of age, in those with baseline creatinine <50 mL/min, in those with a baseline APACHE score >10 and in those with bowel site as the primary site of infection in both groups; however, the cure rates in the ceftolozane/tazobactam plus metronidazole group was approximately 10% lower than those of the meropenem arm in these patients. Older patients usually had more than one risk factor (lower creatinine clearance, bowel site of infection, APACHE score >10).*

In all the regions, cure rates favored meropenem. The differences in clinical cure rates between treatment arms were similar in the two regions that enrolled the most patients, Eastern Europe and South America (86.2% versus 91.2% and 94.4% versus 91.1% for ceftolozane/tazobactam plus metronidazole versus meropenem treatment arms, respectively). Clinical cure rates in other regions (North America, Rest of World, and Western Europe) were lower compared with Eastern Europe and South America with larger treatment difference between the 2 treatment arms (65.4% vs 76% in ceftolozane/tazobactam plus metronidazole vs. meropenem in North America, 45.5% vs. 52.6% in Western Europe, respectively, and 57.9% vs 65% in Rest of the World, respectively). These subgroups had relatively smaller sample sizes than Eastern Europe and South America and wider confidence intervals. No significant imbalance in baseline characteristics was observed in association with the lower cure rates in the North America and Western Europe regions.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose-ranging trial was done. All patients in the Phase 3 clinical trials for cUTI and for cIAI received the received the same dose of ceftolozane/tazobactam in phase 3 (with adjustments for renal function).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Studies that explore the persistence of efficacy and/or tolerance effects were not performed in the Phase 3 clinical trials as cephalosporins do not demonstrate these drug effects. Ceftolozane/tazobactam indications are the treatment of cUTI and cIAI, which are acute and severe infections that require a short term treatment of not more than 14 days. Therefore, studies of persistence of efficacy and tolerance effects are not necessary.

6.1.10 Additional Efficacy Issues/Analyses

A number of additional sensitivity analyses were performed for the primary efficacy endpoint by the statistical reviewer, Dr. Christopher Kadoorie. All these analyses confirmed that ceftolozane/tazobactam met the primary efficacy endpoint within the 10% non-inferiority margin. Please refer to his review for more details.

6.2 Treatment of Complicated Urinary Tract Infections

Please refer to Section 5.3 for a description of the data pooling of the original two phase 3 studies, and an overview of the study design. In the subsections below, the methodology used in the study is discussed in more detail.

6.2.1 Methods

Study Design

This was a multicenter, prospective, randomized, double-blind, double-dummy Phase 3 study comparing IV ceftolozane/tazobactam (1.5 gm every 8 hours) versus IV levofloxacin 750 mg once daily in the treatment of adults with cUTI/pyelonephritis. The primary objective was to demonstrate non-inferiority of ceftolozane/tazobactam to levofloxacin based on the difference in composite microbiologic eradication and clinical cure rate in the microbiologic ITT population at the TOC visit (7+/-2 days after last dose). The NI margin was specified at 10%, with one sided 0.025 significance level.

Two Phase 3 trials, CXA-cUTI-10-04 and -05 were initially planned, each with a sample size of 776 subjects. Following the release of FDA guidance for complicated intra-abdominal infections (cIAI) indicating that a single large study in IAI could serve as confirmatory evidence for a single cUTI study, data from the 2 identical protocols were pooled and the total sample was revised to 954 patients.

Patients with cUTI or pyelonephritis were randomized in 1:1 ratio to receive either ceftolozane/tazobactam or levofloxacin intravenously for 7 days. Randomization was initially stratified by study site for each protocol, and later amended to stratification by region after pooling the two protocols. Patients were hospitalized for the duration of IV therapy, and those requiring urinary procedures were allowed to receive 9 days of study treatment. At selected sites,

clinically stable patients could be discharged from the hospital after completion of at least 9 doses (3 days) of study drug if arrangements were made for continued outpatient IV administration.

A urine culture was obtained within 36 hours of study drug administration. Investigators could enroll a patient before the culture results were known, but if the culture did not meet the definition of a qualifying pretreatment culture, the patient was withdrawn from the study therapy but followed for safety. Polymicrobial urine cultures in non-catheterized subjects were considered contaminated unless an isolate grew to $>10^5$ CFU/mL or was also isolated from blood culture obtained at same visit. Pre-treatment blood cultures were required in catheterized patients. In all subjects, coagulase negative staphylococci and non-Group D streptococci were not considered uropathogens.

Clinical and microbiologic assessments were done at EOT (within 24 hours after last dose of study drug), at the TOC visit (7 +/-2 days after the last dose of study drug) and the Late Follow Up visit (21 to 42 days after last dose of study drug). Patients were also required to complete a Patient Symptom Questionnaire at the TOC visit.

Inclusion Criteria

1. Able to provide written informed consent
2. At least 18 years of age.
3. Non-lactating female, and if of childbearing potential, must use a barrier method of birth control plus oral or parenteral contraceptives or is abstinent during treatment and for at least 35 days after last dose or has a vasectomized partner
4. Males were required to practice reliable birth control methods during the study and for at least 35 days after last dose of study medication.
5. Pyuria (white blood cell count > 10/μL in unspun urine or ≥ 10 per high power field in spun urine)
6. Clinical signs and/or symptoms of cUTI, either of:
    a. Pyelonephritis, as indicated by at least 2 of the following:
        i. Documented fever (oral temperature > 38°C) accompanied by subject symptoms of rigors, chills, or warmth
        ii. Flank pain
        iii. Costovertebral angle tenderness or suprapubic tenderness on physical exam
        iv. Nausea or vomiting

OR

    b. Complicated lower UTI, as indicated by at least 2 of the following new or worsening symptoms of cUTI:
        i. Dysuria
        ii. Urinary frequency or urinary urgency;
        iii. Documented fever (oral temperature > 38°C) accompanied by subject symptoms of rigors, chills, or warmth;
        iv. Suprapubic pain or flank pain;

v. Costovertebral angle tenderness or suprapubic tenderness on physical exam
vi. Nausea or vomiting;

PLUS, at least 1 of the following complicating factors:

vii. Males with documented history of urinary retention;
viii. Indwelling urinary catheter that was scheduled to be removed during IV study therapy and before the EOT;
ix. Current obstructive uropathy that was scheduled to be medically or surgically relieved during IV study therapy and before the EOT; or
x. Any functional or anatomical abnormality of the urogenital tract (including anatomic malformations or neurogenic bladder) with voiding disturbance resulting in at least 100 mL residual urine.

7. Has a pretreatment baseline urine culture specimen obtained within 24 hours before the start of administration of the first dose of study drug
8. Requires IV antibacterial therapy for the treatment of the presumed cUTI

Exclusion Criteria

1. Has a documented history of any moderate or severe hypersensitivity or allergic reaction to any β-lactam or quinolone antibacterial
2. Has a concomitant infection at the time of randomization, which required nonstudy systemic antibacterial therapy in addition to IV study drug therapy. Drugs with only Gram-positive activity, such as vancomycin or linezolid were allowed.
3. Receipt of any amount of potentially therapeutic antibacterial therapy after collection of the pretreatment baseline urine culture and before administration of the first dose of study drug
4. Receipt of any dose of a potentially therapeutic antibacterial agent for the treatment of the current UTI within 48 hours before the study-qualifying pretreatment baseline urine was obtained. (Subjects receiving current antibiotic prophylaxis for cUTI who presented with signs and symptoms consistent with an active new cUTI were possibly enrolled provided all other eligibility criteria were met including obtaining a pre-treatment qualifying baseline urine culture).
5. Intractable urinary infection at baseline that the Investigator anticipated would require more than 7 days of study drug therapy.
6. Complete, permanent obstruction of the urinary tract
7. Confirmed fungal urinary tract infection at time of randomization (with $\geq 10^3$ fungal CFU/mL)
8. Permanent indwelling bladder catheter or urinary stent including nephrostomy
9. Suspected or confirmed perinephric or intrarenal abscess
10. Suspected or confirmed prostatitis
11. Ileal loop or known vesico-ureteral reflux
12. Severe impairment of renal function including an estimated CLCR <30 mL/min, requirement for peritoneal dialysis, hemodialysis or hemofiltration, or oliguria (<20 mL/h urine output over 24 hours)
13. Urinary catheter that was not scheduled to be removed before the EOT

14. Any condition or circumstance that, in the opinion of the Investigator, compromised the safety of the subject or the quality of study data
15. Any rapidly progressing disease or immediately life-threatening illness including acute hepatic failure, respiratory failure, and septic shock
16. Immunocompromising condition, including established AIDS, hematological malignancy, or bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, or the administration of corticosteroids equivalent to or greater than 40 mg of prednisone per day administered continuously for more than 14 days preceding randomization.
17. One or more of the following laboratory abnormalities in baseline specimens: AST, ALT, alkaline phosphatase, or total bilirubin level greater than 3x ULN, absolute neutrophil count less than 500/μL, platelet count less than 40 000/μL, or hematocrit less than 20%
18. Women who were pregnant or nursing.

Patients randomized to ceftolozane/tazobactam received 3 active infusions and one dummy infusion every day, and patients randomized to levofloxacin received 1 active infusion and 3 dummy infusions every day. Ceftolozane/tazobactam (or matching dummy) was infused over one hour; levofloxacin (or matching dummy) was infused over 1.5 hours. Dose adjustments for renal insufficiency were performed by an unblinded pharmacist. Patients who developed CrCl<30 were withdrawn from the study. Dose adjustments were as follows:

Table 24: Dosage Adjustment for Renal Impairment

Cr Clearance	Ceftolozane/Tazobactam	Levofloxacin
> 50	No adjustment	No adjustment
30-50	Decrease dose to 750 mg IV q 8 hours	Decrease to 750 mg every 48 hours
<30	Discontinue	Discontinue

The primary efficacy outcome was the proportion of subjects in the mMITT population who had microbiologic eradication and clinical cure at the TOC visit. The key secondary efficacy outcome was the proportion of patients in the ME population who had microbiologic and clinical cure at the TOC visit. Other outcomes were clinical response at the EOT, TOC and LFU visits, microbiologic response at the EOT, TOC and LFU visits and per-pathogen microbiologic eradication rates.

6.2.2 Demographics

1093 Subjects were enrolled. The analysis populations were defined as follows

Table 25: Definitions of Analysis Populations

Population	Acronym	Definition
Intent-to-Treat	ITT	All randomized patients
Modified ITT	MITT	All randomized patients who received any amount of

		study drug.
Microbiologic MITT	mMITT	All MITT who also had at least one qualified uropathogen from a study-qualifying pretreatment baseline urine specimen.
Clinically Evaluable at Test-of-Cure visit	CE at TOC	All mMITT who • Adhered to study procedures • received the study drug to which they were randomized and had 80-120% study treatment compliance, • had document pyuria at baseline, • presented with s/s indicative of cUTI which included 2 clinical symptoms for pyelonephritis and 2 clinical symptoms plus one complicating factor for cUTI • Had a TOC visit within the specified visit window
Microbiologically Evaluable at Test of Cure	ME at TOC	All CE at TOC who had an appropriately collected and interpretable urine culture at TOC
Clinically Evaluable at Late Follow Up visit	CE at LFU	All CE at TOC who were also clinical cures at TOC and had LFU assessment at 21 to 42 days after the last dose of the study medication.
Microbiologically Evaluable at Late Follow Up visit	ME at LFU	All ME at TOC who also had microbiologic eradication at the TOC visit for each of the baseline infecting pathogen(s) and had LFU assessment.
Safety Population		All subjects who received any amount of study drug*.

* ITT subjects were analyzed according to the study drug they were randomized to. The safety population was analyzed according to the study drug received. If a subject received any amount of both study drugs, they were categorized to the ceftolozane/tazobactam arm.

Table 26: Analysis Populations – Phase 3 Study -cUTI

	Ceftolozane/Tazobactam	**Levofloxacin**
Randomized (ITT)	543	540
MITT	534 (98.3%)	534 (98.9%)
Excluded from MITT Did not receive study drug	9 (1.7%) 9	6 (1.1%) 6
mMITT	398 (73.3%)	402 (74.4%)
Excluded from mMITT No baseline infecting pathogen	136 (25.0%) 136	132 (24.4%) 132
CE at TOC	356 (65.6%)	370 (68.5%)

Excluded from CE at TOC*	42	32
Did not have TOC visit	31	21
Did not meet disease criteria	3	3
Received incorrect drug	1	0
Not compliant	4	9
Confounding efficacy factor	7	5
Urine catheter not removed	3	1
ME at TOC	341 (62.8%)	353 (65.4%)
Excluded from ME at TOC	57	59
Excluded from CE at TOC	42	32
No valid TOC urine culture	12	14
TOC culture not interpretable	3	3
CE at LFU	331 (61.0%)	329 (60.9%)
Excluded from CE at LFU*	25 (4.6%)	41 (7.6%)
Did not have LFU visit	11	19
Clinical failure/indeterminate	*15 (2.7%)*	*28 (5.2%)*
Clinical failure after TOC	0	0
Indeterminate at LFU	4	4
Confounding medication prior to LFU	6	4
ME at LFU	58 (10.7%)	48 (8.9%)
Excluded from ME at LFU	283	305
Excluded from ME at TOC	57	59
Micro failure/indeterminate at TOC	*47 (8.7%)*	*79 (14.6%)*
No LFU 21-42 days	250 (46.0%)	258 (47.8%)
Safety	533** (98.2%)	535 (98.2%)

*Some subjects had more than one reason for exclusion
**One subject (1004-6603-001) randomized to Ceftolozane/Tazobactam received levofloxacin. This subject was included in ceftolozane/tazobactam MITT population but in the safety levofloxacin population.

Table 27: Patient Characteristics – MITT – Phase 3 Study- cUTI

	Ceftolozane/Tazobactam N = 534	**Levofloxacin N = 534**
Age		
Mean (SD)	49.6 (19.5)	48.6 (20.1)
Median (Range)	52 (18-91)	51 (18-87)
Age group		
≥18-<45	216 (40.4%)	237 (44.4%)
≥45-<65	184 (34.5%)	157 (29.4%)
≥65-<75	77 (14.4%)	80 (15.0%)
≥75	57 (10.7%)	65 (12.2%)
Male	159 (29.8%)	155 (29.0%)

Female	375 (70.2%)	379 (71.0%)
Race		
White	450 (84.3%)	463 (86.7%)
Black	8 (1.5%)	6 (1.1%)
Asian	50 (9.4%)	44 (8.2%)
Other	26 (4.9%)	21 (3.9%)
Ethnicity		
Hispanic or Latino	64 (12.0%)	65 (12.2%)
Non-Hispanic	435 (81.5%)	431 (8.1%)
Not Applicable	35 (6.5%)	38 (7.1%)
Region		
Eastern Europe	401 (75.1%)	403 (75.5%)
North America	22 (4.1%)	24 (4.5%)
South America	45 (8.4%)	45 (8.4%)
Rest of World	66 (12.4%)	62 (11.6%)
Country		
Brazil	9	8
Bulgaria	8	6
Chile	0	1
Colombia	20	21
Croatia	6	6
Estonia	14	13
Georgia	30	30
Hungary	35	34
India	21	17
Israel	11	13
Latvia	26	27
Mexico	12	15
Moldova	8	9
Peru	16	15
Poland	39	37
Romania	58	56
Russian Federation	87	100
Serbia	3	2
Slovakia	2	3
Slovenia	4	3
South Africa	6	6
South Korea	7	8
Thailand	21	18
Ukraine	81	77
United States	10	9
BMI		
Mean (SD)	25.7 (5.7)	26.0 (5.5)
Median (Range)	24.8 (15.8-55.3)	25.1 (15.3-53.2)

CrCl at Baseline		
≥80 mL/min	336 (62.9%)	354 (66.3%)
>50-<80 (mild impairment)	147 (27.5%)	141 (32.0%)
≥30-≤50 (moderate)	44 (8.2%)	38 (7.2%)
<30 (severe)	5 (0.9%)	1 (0.2%)
Diagnosis		
Pyelonephritis	421 (78.8%)	420 (78.7%)
cUTI	113 (21.2%)	114 (21.2%)

Reviewer's Comments
The treatment arms were balanced as to mean and median age, age groups, sex, race, ethnicity, BMI, proportion with renal impairment and proportion of patients with pyelonephritis or cUTI. As expected from the epidemiology of urinary tract infections, more females than males were enrolled. Approximately 85% of patients were white, reflecting the fact that the largest proportion of subjects (75%) was enrolled in Eastern Europe.

Table 28: Subject Characteristics – mMITT – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 398	**Levofloxacin N = 402**
Age		
Mean (SD)	49.1 (19.7)	48.1 (20.2)
Median (Range)	51.0 (18-90)	49.5 (18-87)
Age group		
≥18-<45	165 (41.4%)	182 (45.3%)
≥45-<65	133 (33.4%)	121 (30.1%)
≥65-<75	57 (14.3%)	53 (13.2%)
≥75	43 (10.8%)	46 (11.4%)
Male	105 (26.4%)	103 (25.6%)
Female	293 (73.6%)	299 (74.4%)
Race		
White	340 (85.4%)	346 (86.1%)
Black	6 (1.5%)	6 (1.5%)
Asian	34 (8.5%)	33 (8.2%)
Other	18 (4.5%)	17 (4.2%)
Ethnicity		
Hispanic or Latino	46 (11.6%)	48 (11.9%)
Non-Hispanic	331 (83.2%)	330 (82.1%)
Not Applicable	21 (5.3%)	24 (6.0%)
Region		
Eastern Europe	304 (76.4%)	304 (75.6%)
North America	15 (3.7%)	10 (2.5%)
South America	32 (8.0%)	40 (10.0%)
Rest of World	47 (11.0%)	48 (12.0%)

Country		
Brazil	3	7
Bulgaria	7	6
Chile	0	1
Colombia	18	19
Croatia	5	6
Estonia	10	10
Georgia	20	25
Hungary	31	29
India	12	13
Israel	9	11
Latvia	16	21
Mexico	6	5
Moldova, Republic Of	6	4
Peru	11	13
Poland	31	26
Romania	40	38
Russian Federation	55	60
Serbia	2	2
Slovakia	2	0
Slovenia	4	1
South Africa	5	5
South Korea	6	6
Thailand	15	13
Ukraine	75	76
United States	9	5
BMI		
Mean (SD)	25.5 (6.8)	26.1 (5.6)
Median (Range)	24.7 (15.8-55.3)	25.3 (15.3-53.2)
CrCl at baseline		
≥80 mL/min	247 (62.1%)	274 (68.2%)
>50-<80 (mild impairment)	116 (29.1%)	100 (24.9%)
≥30-≤50 (moderate)	31 (7.8%)	27 (6.7%)
<30 (severe)	3 (0.8%)	1 (0.2%)
Diagnosis		
Pyelonephritis	328 (82.4%)	328 (81.6%)
cUTI	70 (17.6%)	74 (18.4%)

Reviewer's Comments: The treatment arms in the mMITT population remained balanced as to age, sex, race, ethnicity, BMI, proportion with renal impairment and proportion with pyelonephritis or cUTI.

Table 29: Baseline Clinical Signs and Symptoms mMITT – Phase 3 Study - cUTI

Clinical Signs and symptoms	Ceftolozane/Tazobactam N = 398	Levofloxacin N = 402
Subjects with Pyelonephritis	**328 (82.4%)**	**328 (81.6%)**
Fever, rigors, chills	258 (78.7%)	267 (81.4%)
Flank pain	313 (95.4%)	312 (95.1%)
CV or suprapubic tenderness	298 (90.9%)	297 (90.5%)
Nausea or vomiting	175 (53.4%)	171 (52.1%)
Subjects with cUTI	**70 (17.6%)**	**74 (18.4%)**
Dysuria/frequency/or urgency	64 (91.4%)	69 (93.2%)
Fever, rigors, chills	17 (24.3%)	16 (21.6%)
Suprapubic or flank pain	61 (87.1%)	70 (94.6%)
CV or suprapubic tenderness	53 (75.7%)	58 (78.4%)
Nausea or vomiting	19 (27.1%)	9 (12.2%)
Males with urinary retention	35 (50.0%)	28 (37.8%)
Indwelling catheter	10 (14.3%)	6 (8.1%)
Obstructive uropathy	9 (12.9%)	9 (12.2%)
Anatomic GU abnormality	35 (50.0%)	45 (60.8%)

Reviewer's Comments: The treatment arms were balanced as to baseline signs and symptoms, and the presence of urinary catheter, urinary obstruction, or structural GU abnormality.

Table 30: Baseline Urinary Pathogens mMITT – Phase 3 Study - cUTI

Urinary Pathogens	Ceftolozane/Tazobactam N = 398	Levofloxacin N = 402
Gram Negative Aerobes	378 (95.0%)	386 (96.0%)
Enterobacteriaceae	369 (92.7%)	370 (92.0%)
E. coli	305 (76.6%)	324 (80.6%)
K. pneumoniae	33 (8.3%)	25 (6.2%)
P. mirabilis	12 (3.0%)	12 (3.0%)
Enterobacter spp.	10 (2.5%)	9 (2.2%)
Other *Enterobacteriaceae**	12 (3.0%)	7 (1.7%)
P. aeruginosa	8 (2.0%)	15 (3.7%)
Other**	2 (0.5%)	1 (0.2%)
Gram Positive Aerobes	25 (6.3%)	23 (5.7%)
E. faecalis	20 (5.0%)	18 (4.5%)
Other[¥]	6 (1.5%)	5 (1.2%)

Some subjects had more than one qualifying pathogen isolated
**Serratia, Pantoea, Morganella, Citrobacter*
***Acinetobacter, Pseudomonas spp., Xanthomonas maltophilia*
[¥]*E. faecium, Staphylococcus aureus*

Table 31: Baseline Blood Pathogens – mMITT – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 398	**Levofloxacin N = 402**
Subjects with bacteremia	29 (7.3%)	33 (8.2%)
Gram Negative Aerobes	23	27
Enterobacteriaceae	22	26
E. coli	19	21
Other *Enterobacteriaceae**	4	6
Gram Positive Aerobes**	6	7
Gram Positive Anaerobes[¥]	1	0

**Klebsiella, Pantoea, Citrobacter, Proteus, Yersinia*
**Coagulase-negative *Staphylococcus*, alpha-hemolytic *Streptococcus*
[¥]*P. acnes*

Reviewer's Comments
As expected, the majority of infections were due to Enterobacteriaceae, most frequently E. coli. The pattern of microbial isolates was balanced between the two treatment arms. The frequency of bacteremia and nature of isolated pathogens was also balanced at baseline.

Table 32: Baseline Susceptibility to Ceftolozane/Tazobactam in Both Treatment Arms – mMITT - Phase 3 Study- cUTI

	Ceftolozane/Tazobactam					**Levofloxacin**				
	N*	S	I	R		N*		S	I	R
Gram Negative Aerobes	364	350	4	10 (2.7%)		367		356	1	10 (2.7%)
E. coli	292	290	0	2 (0.7%)		353		348	1	4 (1.1%)
K. pneumoniae	30	27	1	2 (6.7%)		25		21	0	4 (16.0%)
P. mirabilis	12	12	0	0		11		11	0	0
Enterobacter spp.	10	6	2	2 (20.0%)		9		9	0	0
P. aeruginosa	8	4	1	2 (25.0%)		13		8	0	5 (38.5%)
E. faecalis	18	0	0	18 (100%)		17		0	0	17 (100%)

*Number of isolates for which susceptibility results were reported
S = Susceptible, I = intermediate, R = resistant

Table 33: Baseline Susceptibility to Levofloxacin in Both Treatment Arms - mMITT – Phase 3 Study -cUTI

	Ceftolozane/Tazobactam					**Levofloxacin**				
	N*	S	I	R		N*		S	I	R
Gram Negative Aerobes	364	265	8	91 (25.0%)		367		252	11	104 (28.3%)
E. coli	305	221	5	66 (21.6%)		302		219	5	78 (25.8%)
K. pneumoniae	30	15	2	13 (43.3%)		25		11	3	11 (44.0%)
P. mirabilis	12	12	0	0		11		7	2	2 (18.2%)

Enterobacter spp.	6	5	0	5 (83.3%)		9		5	1	3 (33.3%)
P. aeruginosa	7	2	1	4 (57.1%)		13		5	0	8 (61.5%)
E. faecalis	18	7	1	10 (55.6%)		17		8	0	9 (52.9%)

*Number of isolates for which susceptibility results were reported

Reviewer's Comments
Approximately 3% of Gram negative isolates in each treatment arm were resistant to ceftolozane/tazobactam at baseline. The frequency of resistance to ceftolozane/tazobactam among E. coli isolates was low (6/694, 0.9%). The frequency of baseline resistance was greatest for P. aeruginosa (7/21, 33.3%), K. pneumoniae (6/55, 11%) and Enterobacter spp. (2/19, 10.5%).
As expected, all E. faecalis isolates were resistant to ceftolozane/tazobactam.

In comparison, 25-28% of Gram negative isolates were resistant to levofloxacin at baseline. 23.7% of baseline E. coli isolates were resistant. The prevalence of resistance to levofloxacin among P. aeruginosa, Enterobacter spp., and K. pneumoniae was 60%, 53% and 44% respectively. Approximately 55% of Enterococcus isolates were resistant.

32 subjects had received antibacterial medication prior to enrollment, 19 (4.8%) in the ceftolozane arm and 13 (3.2%) in the levofloxacin arm. One subject in the ceftolozane/tazobactam arm received a first generation cephalosporin 1 day prior to enrollment; all others received the antibacterial medication at least 3 days prior to enrollment.

6.2.3 Patient Disposition

A total of 1083 patients were randomized: 812 in Eastern Europe, 50 in North America, 91 in South America and 130 in the rest of the world.

Table 34: Patient Disposition – ITT – Phase 3 Study -cUTI

	Ceftolozane/Tazobactam	**Levofloxacin**
Randomized	543	540
Dosed (Safety Population)	534 (98.3%)	534 (98.9%)
Completed Study	513 (94.5%)	515 (95.4%)
Completed Study Drug	410 (75.5%)	399 (73.9%)
Prematurely withdrew from Study	29 (5.3%)	25 (4.6%)
Subject decision	13	10
Lost to follow up	9	10
Lack of informed consent	1	0
Adverse event	0	1
Other	7	4

Prematurely Discontinued Study Drug	124 (22.8%)	135 (25.0%)
Lack of qualifying pre-Rx culture	97	93
Subject decision	12	15
Adverse event	7	9
Lack of efficacy	3	6
Major protocol violation	3	4
Other	2	8

Reviewer's Comments: The two arms were balanced as to the proportion of subjects who withdrew from the study and the reasons for withdrawal.

Protocol Deviations

6 patients who had severe renal impairment were enrolled (5 vs 1). One ceftolozane/tazobactam patient withdrew after 4 doses because of worsening renal function (1004-4005-003), one was discontinued (005-5006-001), and one was discontinued due to negative urine culture (1005-5602-003). The others completed study treatment and study (1004-8033-002, 1005-8137-013 and 1005-5302-001).

No unblinding occurred due a medical emergency. CRO staff were accidently unblinded for one patient at each of three sites, and study site staff were accidently unblinded for one patient at each of 3 sites and 2 subjects at one site. None of the patients was discontinued due to accidental unblinding.

A finding of GCP noncompliance with potential risk for data integrity was reported in an applicant audit, conducted after the enrollment had closed, at site number 5609 involving 6 patients (10055609-001, 1005-5609-002, 1005-5609-003, 1005-5609-004, 1005-5609-005, and 10055609-006). The sponsor conducted efficacy analysis including and excluding these 6 patients.

Reviewer's Comments: The protocol violations are not expected to change the safety or efficacy assessments.

6.2.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the composite microbiologic and clinical cure rates at the TOC visit. The primary analysis was in the mMITT population and the secondary analysis was in the ME population.

34 patients, 17 (4.3%) in the ceftolozane arm and 17 (4.2%) in the levofloxacin arm received a concomitant antibacterial medication. 27 of these 34 patients, 13 in the ceftolozane arm and 14 in the levofloxacin arm received a potentially effective antibacterial during the time period of start of therapy until TOC. These were designated failures or indeterminate for the primary outcome. In all cases, the cited reason for the concomitant antibacterial was ongoing signs and symptoms of pyelonephritis or cUTI.

Table 35: Composite Cure at TOC visit – mMITT – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 398	Levofloxacin N = 402	Difference (95% CI)
Composite Cure	306 (76.9%)	275 (68.6%)	8.5 (2.31, 14.57)*
Failure	66 (16.6%)	103 (25.6%)	
Indeterminate	26 (6.5%)	24 (6.0%)	

*The 99% CI for the difference was (0.36, 16.46)

Table 36: Composite Cure at TOC Visit-ME Population – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 341	Levofloxacin N = 353	Difference 95% CI
Cure	284 (83.3%)	266 (75.4%)	8.0 (1.95, 13.97)*
Failure	57 (16.7%)	87 (24.6%)	

*The 99% CI for the difference was (0.01, 15.84)

Table 37: Composite Response by Subgroups – mMITT – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 398	Levofloxacin N = 402	Difference 95% CI
Composite Cure	306 (76.9%)	275 (68.6%)	8.5 (2.3, 14.6
Age Groups (Years)			
≥18 to <45	142/165 (86.1%)	141/182 (77.5%)	8.6 (0.4, 16.6)
≥45 to <65	94/133 (70.7%)	81/182 (66.9%)	3.7 (-7.6, 15.0)
≥65	70/100 (70.0%)	53/99 (53.5%)	16.5 (3.0, 29.2)
Sex			
Male	69/105 (65.7%)	59/103 (57.6%)	8.1 (-4.8,21.4)
Female	237/293 (80.9%)	216/299 (72.2%)	8.7 (1.8,15.4)
Region			
Eastern Europe	235/304 (77.3%)	213/304 (70.1%)	7.2 (0.2, 14.2)
North America	8/15 (53.3%)	8/10 (80.0%)	-26.7 (-53.9, 11.3)
South America	26/32 (81.3%)	23/40 (57.5%)	23.8 (2.1, 41.9)
Rest of World	37/47 (78.7%)	31/48 (64.6%)	14.1 (-4.01, 31.06)
Diagnosis			
Pyelonephritis	259/328 (79.0%)	240/328 (73.2%)	5.8 (-0.7, 12.3)
cUTI	47/70 (67.1%)	35/74 (47.3%)	19.8 (3.7, 34.6)
Cr Clearance			
>50	285/363 (78.5%)	258/374 (69.0%)	9.5 (3.2, 15.8)
≤50	21/34 (61.8%)	17 (60.7%)	1.1 (-21.9, 24.3)
Bacteremia at Baseline			
Yes	23/29 (79.3%)	19/33 (57.6%)	21.7 (-1.6, 41.7)

No	283/269 (76.6%)	256/369 (69.4%)	7.3 (0.9, 13.6)
ESBL Producer			
ESBL Producer	38/61 (62.3%)	20/57 (35.1%)	27.2 (3.5, 47)
Levofloxacin Resistant Baseline Pathogen			
Resistant	60/100 (60.0%)	44/112 (39.3%)	20.7 (7.2, 33.2)
Susceptible	231/272 (84.9%)	210/259 (81.8%)	3.8 (-2.6, 10.3)
Race			
White	261/340 (76.8%)	239/346 (69.1%)	7.7 (1.0,14.3)
Black	5/6 (83.3%)	3/6 (50.0%)	33.3 (-20.0,71.8)
Asian	27/34 (79.4%)	23/33 (69.7%)	9.7 (-11.3,30.3)
Other	13/18 (72.2%)	10/17 (58.8%)	13.4 (-17.8,42.5)
Protocol			
Protocol 1004	145/198 (73.2%)	145/205 (70.7%)	2.5 (-6.3,11.2)
Protocol 1005	161/200 (80.5%)	130/197 (66.0%)	14.5 (5.9, 23.1)

Reviewer's Comments: *The 99% CI for the difference in response suggests that ceftolozane/tazobactam is superior to levofloxacin. However, the proportion of isolates that were resistant to levofloxacin at baseline was considerably higher in the levofloxacin arm compared to the proportion of isolates that were resistant to ceftolozane at baseline in the ceftolozane arm (28% vs. 3%) indicating that 97% of subjects in the ceftolozane/tazobactam arm received an antimicrobial to which the organism was susceptible, and 72% of subjects in the levofloxacin arm received an antimicrobial to which the organism was susceptible.*

Among patients with baseline levofloxacin resistance, ceftolozane/tazobactam was superior to levofloxacin for the composite cure and also for clinical cure and microbiologic cures individually. Among patients with baseline levofloxacin susceptible organisms, ceftolozane was non-inferior to levofloxacin for the composite cure and also non-inferior for clinical cure and microbiologic cures individually (see tables below). The conclusion of superiority in the overall population is driven by the superiority in the levofloxacin resistant group.

Table 38: Outcomes at TOC in Subjects with a Baseline Pathogen Resistant to Levofloxacin – mMITT – Phase 3 Study - cUTI

Efficacy Endpoint	***Ceftolozane/ Tazobactam N = 100***	***Levofloxacin N= 112***	***Difference (95% CI)***
Microbiological success	*63/100 (63.0%)*	*49/112 (43.8%)*	*19.2 (5.8 , 32.0)*
Clinical Cure	*90/100 (90.0%)*	*86/112 (76.8%)*	*13.2 (3.2 , 23.2)*
Composite Cure	*60/100 (60.0%)*	*44/112 (39.3%)*	*20.7 (7.2, 33.2)*

Table 39: Outcomes at TOC in Subjects with a Baseline Pathogen Susceptible to Levofloxacin – mMITT – Phase 3 Study - cUTI

Efficacy Endpoint	***Ceftolozane/ Tazobactam N = 298***	***Levofloxacin N = 290***	***Difference (95% CI)***
Microbiological success	*257/298 (86.2%)*	*241/290 (83.1%)*	*3.1 (-2.7 , 9.0)*
Clinical Cure	*276/298 (92.6%)*	*270/290 (93.1%)*	*-0.5 (-4.8 to 3.8)*
Composite Cure	*231/272 (84.9%)*	*210/259 (81.1%)*	*3.8 (-2.6, 10.3)*

Reviewer's Comments*: Ceftolozane/tazobactam was superior to levofloxacin in the subset of patients who had an ESBL producing organism at baseline (62% vs. 35% composite cure). This is also explained by the high prevalence of baseline levofloxacin resistance among ESBL producers. Of the 57 patients in the levofloxacin arm who had an ESBL producer at baseline, only 7 (12.3%) were susceptible to levofloxacin, 45 (79%) were resistant and 5 (8.8%) were intermediate. In comparison, of the 61 patients in the ceftolozane/tazobactam arm who had an ESBL producer at baseline, 49 (80%) were susceptible to ceftolozane/tazobactam, 9 (15%) were resistant and 3 (5%) were intermediate. However, the response rates indicate that ceftolozane/tazobactam is an efficacious option in the treatment of ESBL producing organisms, which tend to also be multi-drug resistant.*

The difference in response was numerically higher among patients who were enrolled under protocol 1005 compared to those enrolled under protocol 1004. This is also accounted for by the higher proportion of patients enrolled under protocol 1005 who had levofloxacin resistance at baseline; the proportion of levofloxacin recipients who had levofloxacin resistant isolates at baseline was 34% in protocol 1005 compared to 21% in protocol 1004.

The proportion of patients with composite cure was consistently numerically higher among ceftolozane/tazobactam recipients compared to levofloxacin recipients in all subgroups and in all regions except in North America. The number of patients enrolled in North America was small (25 subjects in mMITT, 14 in the US and 11 in Mexico), and there are no theoretical reasons that are likely to impact the applicability of foreign data to US patients.

6.2.5 Analysis of Secondary Endpoints(s)

Table 40: Clinical and Microbiologic Response EOT – mMITT and ME Populations – Phase 3 Study –cUTI

	Ceftolozane/Tazobactam	**Levofloxacin**	**Difference 95% CI**
mMITT	N = 398	N = 402	
Clinical Cure	375 (94.2%)	371 (92.3%)	1.9 (-1.60, 5.50)
Microbiologic Cure	379 (95.2%)	340 (84.6%)	10.6 (6.55,14.86)

ME	N = 341	N = 353	
Clinical Cure	332 (97.4%)	341 (96.6%)	0.8 (-1.9, 3.5)
Microbiologic Cure	329 (96.5%)	300 (85.0%)	11.5 (7.3, 15.8)

Table 41: Clinical and Microbiologic Response TOC - mMITT – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 398	**Levofloxacin N = 402**	**Difference 95% CI**
Clinical Cure	366 (92.0%)	356 (88.6%)	3.4 (-0.74, 7.57)
Pyelonephritis	306/328 (93.3%)	295/328 (89.9%)	3.4 (-0.93, 7.70)
cUTI	60/70 (85.7%)	61/74 (82.4%)	3.3 (-8.97, 15.29)
Microbiologic Cure	320 (80.4%)	290 (72.1%)	8.3 (2.37, 14.09
Pyelonephritis	270/328 (82.3%)	253/328 (77.1%)	5.3 (-0.98, 11.31)
cUTI	50/70 (71.4%)	37/74 (50.0%)	21.4 (5.46, 35.88)

Reviewer's Comments*: Clinical cure was similar for ceftolozane/tazobactam and levofloxacin at EOT. Clinical cure was also similar at TOC visit in the overall population and in subjects with either pyelonephritis or cUTI.*

For microbiologic cure, ceftolozane/tazobactam seemed superior to levofloxacin in the overall population and in the subpopulation of patients with cUTI, and similar in the subpopulation with pyelonephritis. This is explained by the prevalence of levofloxacin resistance at baseline, which was higher among cUTI patients compared to pyelonephritis patients; 64/144, 44.5% of cUTI patients had a levofloxacin resistant organism compared to 146/656, 22.2% of pyelonephritis patients.

6.2.6 Other Endpoints

Table 42: Sustained Clinical and Microbiologic Response at LFU visit – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 398	**Levofloxacin N = 402**	**Difference 95% CI**
Clinical Cure – CE at LFU Population	319/331 (96.4%)	314/329 (95.4%)	0.9 (-2.22, 4.15)
Microbiologic Cure – ME at LFU Population	41/58 (70.7%)	39/48 (81.3%)	-10.6 (-25.88, 6.07)

Reviewer's Comments
Sustained clinical and microbiologic cures were similar in the two treatment arms.

Table 43: Per Pathogen Eradication Rates at TOC visit – Phase 3 Study - cUTI

	Ceftolozane/ Tazobactam N = 341	**Levofloxacin N = 353**	**Difference 95% CI**
E. coli	237/262 (90.5%)	226/284 (79.6%)	10.9 (4.9, 16.8)
E. coli ESBL	27/36 (75.0%)	18/36 (50.0%)	
E. coli CTX-M-14/15	20/27 (74.1%)	13/25 (52.0%)	
K. pneumoniae	21/25 (84.0%)	14/23 (60.9%)	23.1 (-2.1, 45.4)
K. pneumoniae ESBL	7/10 (70.0%)	2/7 (28.6%)	
K. pneumoniae CTX-M-14/15	5/8 (62.5%)	1/4 (25.0%)	
P. mirabilis	10/10 (100%)	8/11 (72.7%)	27.3 (-5.6, 56.7)
P. aeruginosa	6/7 (85.7%)	7/12 (58.3%)	27.4 (-15.9, 56.3)
E. cloacae	2/6 (33.3%)	6/7 (85.7%)	-52.4 (-78.8, -0.3)
E. faecalis	5/16 (31.3%)	12/16 (75.0%)	-43.8 (-66.4, -9.2)
E. faecium	1/2 (50.0%)	3/3 (100%)	-50.0 (-90.5, 19.3)

Reviewer's Comments
ESBL producing organisms tend to be also multi-drug resistant. There was a high prevalence of levofloxacin resistance among ESBL producers in this study. The higher response rates in the ceftolozane/tazobactam arm indicate that it is an effective option in the treatment of these organisms.

Emergence of Resistance
Three (3) patients in ceftolozane/tazobactam arm (0.7%) had emergence of a gram negative pathogen with decreased susceptibility to the drug, one *P. aeruginosa* and two *E. coli*. Fourteen (14) patients in the levofloxacin arm (3.5%) had emergence of a pathogen with decreased susceptibility to the drug, one *Enterococcus* and *13 E. coli*.

Two patients in the ceftolozane/tazobactam arm (0.5%) had emergence of resistance, one *E. coli* and one *P. aeruginosa*. Sixteen (16) in the levofloxacin arm (4.0%) had emergence of a resistant pathogen, 15 *E. coli* and one *Enterococcus*.

Superinfections and New Infections
Superinfection was defined as urine culture that grew $\geq 10^5$ CFU/mL of a bacterial uropathogen other than the baseline uropathogen(s) during the course of study drug therapy.

New infection was defined as urine culture that grows $\geq 10^5$ CFU/mL of a bacterial uropathogen other than the baseline uropathogen(s) at any time between the last administration of the last dose of study drug therapy and the LFU visit.

Table 44: Superinfections and New Infections – mMITT – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 398	**Levofloxacin N = 402**	**Difference 95% CI**
Superinfections	14 (3.5%)	21 (5.2%)	-1.7 (-4.7, 1.2)
New Infections	36 (9.0%)	27 (6.7%)	2.3 (-1.4, 6.1)

Thirteen of the fourteen superinfections (93%) in the ceftolozane/tazobactam arm were due to an *Enterococcus* species (*faecalis* or *faecium*) compared to 8/21(38%) superinfections in the levofloxacin arm.

Twelve of the 36 (33.3%) new infections in the ceftolozane/tazobactam arm were due to an *Enterococcus spp.*, compared to 11/27 (40.7%) in levofloxacin arm. In either treatment arm, the majority of subjects with new infections did not receive antibacterial therapy for these infections and were reported as clinical cures at TOC suggesting that these new infections were cases of asymptomatic bacteriuria.

6.2.7 Subpopulations

Please refer to table in 6.2.4 for more details. There were no significant differences in efficacy in older patients, however; the higher efficacy rates in the ceftolozane/tazobactam subjects were driven by a higher proportion of levofloxacin resistant organisms at baseline. There were no differences in responses by geographic regions, sex or race.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients in the Phase 3 clinical trials for cUTI received the recommended dosage for ceftolozane/tazobactam.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.2.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

From the analysis of the safety database for the cUTI and cIAI indications, ceftolozane/tazobactam appears to have a similar safety profile to that of the active comparators and to that described for the cephalosporin drug class. Some differences were noted in the safety profile for the cUTI and the cIAI indications. Findings common to both indications and thought to be potentially related to study drug will be described first, followed by a description of those specific to each indication. The most common adverse events (occurring in more than 1% of subjects in the integrated pivotal studies) were nausea, diarrhea, vomiting, headache, pyrexia, constipation, insomnia, transaminase elevations, hypertension and hypokalemia.

Serious adverse events identified as related to ceftolozane/tazobactam were cases of *Clostridium difficile* diarrhea or pseudomembranous colitis, which occurred at low rates, similar to that of the comparators. Regarding specific class-related toxicities, there was a low incidence of Coombs reaction conversion from negative to positive (1 patient in each indication), and in both cases, no manifestation of hemolytic anemia was observed. There were no cases of anaphylactic shock or serious hypersensitivity reactions in the ceftolozane/tazobactam arm in clinical studies. Rashes were observed at a low frequency, similar to that of the comparators. Transaminase elevations were observed during the study; these were transient. No indication of drug-induced liver injury was identified as measured by patients meeting criteria of Hy's law after initiation of study drug in the phase 3 studies. Adverse events indicative of renal impairment were overall low (<1%); however, more patients in the ceftolozane/tazobactam arm discontinued the drug due to worsening renal function. Since the renal system is a target organ for toxicity in nonclinical studies and the only pathway of drug elimination, renal toxicity is likely to be drug related.

In the cIAI indication, ceftolozane/tazobactam plus metronidazole treatment was associated with overall slightly higher rates of adverse events than the comparator, meropenem. They likely reflect the increased morbidity of the study population, associated surgical procedures, the additional number of concomitant medications, including the combination with metronidazole, and of the severity of the underlying infection in patients with several co-morbidities, mainly cardiovascular, metabolic and respiratory conditions. The combination treatment with metronidazole adds complexity to the determination of causality, especially of hepatic and neurological toxicities, which are the most common side effects of metronidazole.

The most common AEs in the cIAI indication were nausea, diarrhea, pyrexia, vomiting and insomnia. Overall, these adverse events rates tended to be higher than those observed in the ceftolozane/tazobactam arm of the cUTI trial.

Infections (4.2% in the ceftolozane/tazobactam plus metronidazole versus 2.3% in meropenem treatment arms) were the most common serious adverse events and included pneumonia, abscess, sepsis and urinary tract infection. All but one case were considered treatment failures in the ceftolozane/tazobactam arm. Thrombocytosis, deep venous thrombosis events, an overall higher number of arrhythmias and a non-statistically significant higher rate of deaths were observed in the ceftolozane/tazobactam plus metronidazole arm. These are known complications of intra-abdominal infections and surgery in subjects with predisposing chronic conditions, mainly cardiac, metabolic and pulmonary diseases, and potentially reflect the relatively lower efficacy of ceftolozane/tazobactam observed, which cannot be ruled out as a contributing factor to the imbalance observed in these events.

Thromboembolic events (including deep vein thrombosis, pulmonary embolism, bowel ischemia, myocardial infarction and stroke) were reported as SAEs in 1.4% of subjects in the ceftolozane/tazobactam plus metronidazole arm and in 0.6% of subjects in the meropenem arm. One SAE of thrombocytosis was observed in the ceftolozane/tazobactam arm without clinical manifestations. The patient had a diagnosis of thrombocytosis in the past, of unclear etiology. A platelet increase more than twice the baseline was observed temporally associated with study drug, returning to baseline after treatment. Thrombocytosis overall was observed at a 1.9% rate versus 1% in the meropenem arm. This difference was not observed in the cUTI trial, where thrombocytosis was observed at a rate of 0.5% in both arms.

Even though all subjects who presented thromboembolic events had other risk factors, a potential drug contribution to these events cannot be completely excluded, since a temporal association was observed in some of them, with progression during antibacterial and anticoagulant treatment. There is insufficient evidence to support a hypothesis about potentially drug-induced hypercoagulability. In addition, there are too many confounding risk factors including concomitant medications, and because these events were not observed in higher frequency in the cUTI study, a drug effect is unlikely. Instead, this increased frequency of thromboembolic events as compared to the meropenem arm may reflect a relatively lower efficacy of ceftolozane/tazobactam in controlling clinical manifestations and complications of the underlying infection. This uncertainty should not preclude approval because the drug will be used for the treatment of life-threatening infections. The mortality rate observed in the ceftolozane/tazobactam plus metronidazole arm is within what is expected and reported previously for this patient population in similar studies. The mortality imbalance with the meropenem arm, a 1% difference, did not reach statistical significance, and reflects a combination of factors, mainly infection and surgery complications and underlying co-morbidities, which were similar in nature to but in slightly higher frequency than those observed in the comparator arm. The deaths were classified as treatment failures or indeterminate, which were counted as failures in the primary efficacy analysis.

From the subgroup analysis in the cIAI indication, there appeared to be a higher incidence of adverse events in older patients with infections originating in the bowel as compared with patients with other primary sites of infection, also among patients with an APACHE II score ≥10 compared with patients with a score <10 in both the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, and in patients with creatinine clearance <50mL, but they were more frequently observed in the ceftolozane/tazobactam plus metronidazole arm than in the meropenem arm. There were several confounding risk factors in the more severely ill patient population that characterizes the cIAI indication, particularly in older patients, and it is not possible to evaluate the contribution of the drug to the causality of these events.

Post-marketing monitoring of thromboembolic events is recommended.

In the cUTI indication, the frequency and nature of adverse events were similar in the two treatment arms. The most common AEs noted were nausea, diarrhea, headache, urinary tract infections and hypertension. Overall, 12/19 and 9/12 of all urinary tract infections in the ceftolozane/tazobactam arm and in the levofloxacin arm, respectively, were treatment failures. The remaining were superinfections or new infections. The rate of SAEs was low and comparable in both arms (15/533 or 2.8% in ceftolozane/tazobactam arm and 18/535 or 3.4% in the levofloxacin arm). Most of the SAEs reported in both arms were infections, most commonly urinary tract infections, and represented treatment failures in the setting of levofloxacin resistance in the levo arm.

Overall, diarrhea was reported more frequently in the levofloxacin arm, and 19/23 (83%) cases in the levofloxacin arm were categorized as drug related by the investigator, compared to 4/10 (40%) cases in the ceftolozane/tazobactam arm. Three cases of *Clostridium difficile* infection (2 CDI and one pseudomembranous colitis) occurred in the ceftolozane/tazobactam arm compared to no cases in the levofloxacin arm. Two of these cases were serious and all 3 were considered drug-related. The study protocol did not require testing for *C. difficile* in the event of diarrhea. It is likely that *C. difficile* cases were underreported and underdiagnosed in both arms.

One death occurred in a 79 year old Polish woman (1005-5802-005) who was diagnosed with unresectable uroepithelial bladder cancer shortly after admission for cUTI. Her comorbidities included type 2 diabetes mellitus, chronic kidney disease, atrial fibrillation, myocardial ischemia and history of carotid endarterectomy. She died on Study Day 43, 38 days after the last dose of ceftolozane/tazobactam. The death is not drug-related.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety analysis set includes all randomized subjects or patients who received any amount of study drug. The primary sources for this clinical safety review consist of the completed studies including 9 Phase 1 studies of ceftolozane alone or ceftolozane/tazobactam in healthy adults and adults with renal impairment; 2 Phase 2 studies, 1 with ceftolozane alone and the other with ceftolozane/tazobactam in patients with cUTI and cIAI, respectively; and 2 large Phase 3 studies of ceftolozane/tazobactam, 1 each in patients with cUTI (pooled data from protocols CXA-cUTI-10-04 and -05) and cIAI (pooled data from protocols CXA-cIAI-10-08 and -09).

Standard safety evaluations were conducted in all studies and included physical examinations, vital signs, and clinical laboratory evaluations, as well as monitoring for AEs and concomitant medication usage. In addition to routine hematology and chemistry safety laboratory tests, a direct Coombs test was included in 8 of the 13 clinical studies. Comprehensive electrocardiogram (ECG) evaluations were conducted in two Phase 1 studies, including the TQT study.

Subjects in the safety population are categorized based on the treatment they received, irrespective of the treatment to which they were randomized. In each indication, one subject who was randomized to ceftolozane/tazobactam actually received the comparator and is, therefore, included in the comparator treatment arm for the safety analysis. One subject (subject 1008-6104-001) who received both treatments was included in the ceftolozane/tazobactam treatment arm; this subject was randomized to the meropenem treatment arm but received ceftolozane/tazobactam for his first dose.
The primary data to support the safety of ceftolozane/tazobactam in subjects with cUTI and cIAI are derived from an integrated analysis of the completed Phase 3 studies. Supportive safety information from the Phase 1 and Phase 2 studies is presented separately as well as serious adverse event (SAE) data from the 1 subject enrolled as of the data cut-off date in the discontinued open-label Phase 3 NP study.

The safety data from the Phase 3 clinical studies were pooled within the indication and then integrated across both indications. The Phase 3 studies were multicenter, randomized, double-blind, active-controlled studies using the same dose of ceftolozane/tazobactam (1.5 g every 8 hours) and had the same safety assessments across indications. The categories for the tabulations of data are based on the following 3 groups:

- Group 1 –Phase 3 cUTI (comprising protocols CXA-cUTI-10-04 and -05)
- Group 2 –Phase 3 cIAI (comprising protocols CXA-cIAI-10-08 and -09)
- Group 3 –Integrated Phase 3 cUTI and cIAI (Group 1 plus Group 2 above)

Safety data from the supportive studies were derived from the individual clinical study reports (CSRs) for these studies. Please refer to Section 5.1 for a list of clinical trials and Section 5.3 for details on the pooling of data and descriptions of the Phase 3 studies.

7.1.2 Categorization of Adverse Events

Throughout the studies, all subjects were monitored for the occurrence of AEs, including possible allergic reactions and intolerance to study drug.

Adverse events were recorded for all subjects from the start of study drug administration through the LFU visit. All AEs occurring from the start of the initial study drug infusion through the LFU evaluation were recorded on the eCRF and assessed for severity, causality, and seriousness.

An AE was defined as any untoward medical occurrence experienced by a subject (whether drug-related or not) receiving a medicinal product in a clinical investigation. In addition, any pre-existing events that increased in severity or changed in nature during, or as a consequence of, use of a medicinal product in a human clinical study were also considered AEs. Post-dose complications that occurred as a result of protocol-mandated procedures (e.g., invasive procedures such as venipuncture and abdominal surgery) were also recorded as AEs. Any overdose, with or without associated AEs, in a clinical study was reported to PRA International, according to the procedures for SAE reporting outlined in the protocol.

A serious adverse event (SAE) was defined as any untoward medical experience that occurred between the time of receiving the first dose of study medication through the LFU evaluation that:

- Results in death;
- Is a life-threatening situation;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability and/or incapacity;
- Is a congenital anomaly and/or birth defect in the offspring of a subject who received study drug.
- Is considered a medically important event.

Any SAE that occurred in that timeframe must have been reported within 24 hours of the time the Investigator or designee became aware that an SAE had occurred, whether or not the event was considered related to study medication.

Throughout the dosing period, all subjects were monitored for AEs at each study visit and had all AEs and SAEs recorded up to the LFU visit. At the TOC visit, all unresolved AEs were followed up by the study staff until resolution or stabilization and any new AEs were recorded. During this follow-up, if any AE worsened and met the criteria for an SAE, this event was recorded as a new SAE. All SAEs were captured from the start of the initial study drug infusion through the LFU evaluation, and followed up until resolution or stabilization.

cIAI Protocol-Specific Exceptions to Serious Adverse Event Reporting to Pharmacovigilance and Other Points to Consider

In this trial, untoward or adverse clinical endpoints were reported in the Clinical Outcome assessments of the eCRF. Regardless of when these events occurred, they were not to be reported as AEs or SAEs in the eCRF and were only to be reported in an expedited manner to Cubist as SAEs in cases of rehospitalization or fatal outcome.

Clinical endpoints not to be reported as AEs are listed below:

1. Lack of efficacy: wound infection, abscess, ongoing or persistent intra-abdominal infection or need for additional antibiotic therapy.

2. Signs, symptoms or laboratory markers of the disease being treated: ongoing or persistent fever or leukocytosis.

For the integrated analysis, in both pivotal cUTI and cIAI studies, AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 14.1. Only treatment-emergent adverse events (TEAEs) were tabulated. A TEAE is defined as an AE that started or a pre-existing condition that worsened, on or after the start (based on date and time) of the first dose of study drug through the last study evaluation.

Treatment-emergent AEs were tabulated by MedDRA system organ class (SOC) and preferred term. Tabulations of TEAEs were produced for all events, as well as by severity, relationship to study drug, time to onset, duration, outcome, and most common events (incidence ≥5%, ≥2%, ≥1%). Summary tables were also produced for SAEs and TEAEs leading to discontinuation of study drug. By-subject listings were provided for TEAEs leading to death, SAEs, TEAEs related to study drug, and TEAEs leading to discontinuation.

Clinical Laboratory Data
All laboratory evaluations (except for serum creatinine for creatinine clearance estimation, serum pregnancy tests, and baseline qualifying test) were performed by the central laboratory. Venous blood samples were obtained at Screening (baseline), Day 3, EOT (unless the same assessment was conducted within the previous 24 hours), TOC, and LFU (if required) except where noted, for the determination of the following laboratory parameters:

Hematology:

- Hemoglobin/hematocrit
- Leukocyte count and differential
- Neutrophils
- Prothrombin time
- Platelet count
- Direct Coombs test

Clinical chemistry:

- Sodium
- Potassium
- Blood urea nitrogen (BUN)
- Chloride
- Creatinine
- Total protein
- Albumin
- Bicarbonate
- Total bilirubin
- Aspartate aminotransferase (AST [SGOT])
- Alanine aminotransferase (ALT [SGPT])
- Alkaline phosphatase (ALP)
- Calcium
- Phosphorus
- Gamma-glutamyl transferase

- Uric acid
- Non-fasting serum glucose
- Human chorionic gonadotropin for females of childbearing potential (local laboratory)

Descriptive statistics were presented for the change from baseline to post-baseline time points as well as the worst post-baseline value (post-baseline maximum and post-baseline minimum) in chemistry and hematology parameters (including coagulation parameters) from the central laboratory data.

Direct Coombs tests were assessed as positive or negative and shifts from baseline (negative to positive or positive to negative) were summarized at end-of-therapy (EOT). The number and percentage of subjects with an unknown result at baseline and with a positive or negative post-baseline result at EOT, as well as the number and percentage of subjects with a positive or negative result at baseline and an unknown post-baseline result at EOT, are also provided.

Laboratory shift tables were constructed for hematology and clinical chemistry parameters. The counts and percentages of subjects for each laboratory parameter are presented in the shift tables. The shift tables describe the shift in toxicity grade from the baseline assessment to post-baseline time points as well as the worst post-baseline assessment across all visits (including unscheduled) according to a modified Division of Microbiology and Infectious Diseases Adult Toxicity Scale, November 2007 criteria.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data from Phase 1, 2 and 3 studies was not done due to differences in study design and endpoints. The two phase 3 studies per indication were pooled for safety and efficacy. Safety results from individual phase 1 and 2 studies are presented separately in section 5.3.

7.2 Adequacy of Safety Assessment

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, the integrated evaluation of safety includes data on 2601 subjects treated with ceftolozane, ceftolozane/tazobactam, or a comparator agent, including placebo, across the Phase 1, 2, and 3 clinical program. A total of 173 subjects received IV ceftolozane alone and 1276 received IV ceftolozane/tazobactam (either as monotherapy or coadministered with metronidazole).

The primary data to support the safety of ceftolozane/tazobactam in subjects with cUTI and cIAI are derived from an integrated analysis of the Phase 3 studies, which includes data from 2047 subjects. Overall in the integrated Phase 3 analysis, 1015 subjects were treated with ceftolozane/tazobactam (with or without metronidazole) and 1032 were treated with a comparator agent (levofloxacin or meropenem). In the integrated analysis, mean duration of therapy was 6.1 days in both the ceftolozane/tazobactam and comparator groups. In the cUTI and cIAI indications, most subjects received 7 days and 4 to 10 days of study therapy, respectively. The exposure for the integrated phase 3 studies is shown in the table below. The extent of exposure to study drug therapy was similar in the ceftolozane/tazobactam and the comparator groups in the Phase 3 studies. Mean exposure to study drug was similar in the two Phase 2 studies.

Table 45: Study Drug Exposure in the Integrated Phase 3 cUTI and cIAI Studies (Safety Population)

Exposure Parameter	Integrated Phase 3 cUTI and cIAI	
	Ceftolozane/Tazobactam (N=1015)	All Comparators (N=1032)
Duration of Exposure		
Mean (SD)	6.07 (2.199)	6.12 (2.115)
Median	6.66	6
Minimum, Maximum	0.05, 13.69	0.01, 13.83
Duration of Exposure (days), n (%)		
>0-<4	68 (6.7)	55
4-<8	362 (35.7)	401
8-<11	522 (51.4)	521
11-<15	58 (5.7)	48
≥15	5 (0.5)	7
Infusion Interrupted, n (%)	12 (1.2)	28

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; n = number of subjects in the specific category; N = number of subjects in the Safety population; SD = standard deviation Source: M5.3.5.3 ISS/Section 2.1/Table 4.

In the cUTI trial, 533 subjects received at least one dose of ceftolozane/tazobactam and 535 received at least one dose of levofloxacin. The mean and median days of therapy received were similar in the two treatment arms.

Table 46: Extent of Exposure – Phase 3 Trial - cUTI

	Ceftolozane/Tazobactam N = 533	**Levofloxacin N = 535**
Duration of Exposure		
Mean, SD	5.8 (1.8)	5.8 (1.7)
Median, Range	6.7 (0.05-8.4)	6.7 (0.01-7.4)
Received		
1-4 days	99 (18.6%)	89 (16.6%)
5-7 days	429 (80.4%)	441 (75.3%)
8-9 days	3 (0.6%)	5 (0.9%)
Missing data	2	0

In the cIAI trial, 482 patients received at least one dose of ceftolozane/tazobactam and 497 received at least one dose of meropenem. The mean and median days of therapy were similar in both treatment arms.

Table 47: Extent of Exposure – Phase 3 -cIAI trial

	Ceftolozane/Tazobactam N = 482	**Meropenem N = 497**
Duration of Exposure		
Mean, SD	6.3 (2.5)	6.4 (2.4)
Median, Range	6.2 (0.07-13.6)	6.1 (0.33-13.8)
Received		
1-<4 days	15 (3.1%)	8 (1.6%)
4-<8 days	231 (47.9%)	250 (50.3%)
8-<11 days	173 (35.9%)	184 (37%)
11<15	58 (12%)	48 (9.7%)
>15	5 (1.0%)	7 (1.4%)

In general, within each indication reasons for premature withdrawal from study drug were similar across the treatment arms. The percentage of subjects prematurely discontinuing study drug was higher in the cUTI indication (24%) than in the cIAI indication (6%) due to the protocol requirement in the cUTI study to discontinue study drug if baseline urine cultures were negative or contaminated. Other reasons for premature discontinuation of study drug were adverse events, which occurred in 7 (1.3%) ceftolozane/tazobactam subjects vs 9 (1.7%) levofloxacin subjects in the cUTI trial and 13 (2.7%) ceftolozane/tazobactam + metronidazole subjects vs. 11 meropenem (2.2%) subjects in the cIAI trial. These adverse events leading to withdrawals from the drug and the study were fatal in 11 patients in the ceftolozane/tazobactam arm in the cIAI trial and in 7 patients in the meropenem arm.

Disposition and Duration of Exposure in the Phase 2 Studies

Across the two Phase 2 studies, 248 subjects received study drug (167 received ceftolozane or ceftolozane/tazobactam). The majority of treated subjects completed study drug treatment (86%)

and no notable differences were observed between treatment arms in treatment completion rates in either Phase 2 study.

Table 48: Subject Disposition in the Phase 2 Studies

Subject Disposition	Study CXA-101-03		Study CXA-IAI-10-01	
	Ceftolozane n (%)	Ceftazidime n (%)	Ceftolozane/ Tazobactam n (%)	Meropenem n (%)
Subjects Randomized	86	43	83	39
Subjects who Received Study Drug	85 (98.8)	42 (97.7)	82 (98.8)	39 (100.0)
Subjects Completing the Study[a]	81 (94.2)	39 (90.7)	78 (94.0)	38 (97.4)
Subjects Prematurely Withdrawn From	5 (5.8)	4 (9.3)	5 (6.0)	1 (2.6)
Serious Adverse Event	0	0	2 (2.4)	0
Physician Decision	0	0	1 (1.2)	0
Withdrew Consent	0	4 (9.3)	1 (1.2)	0
Lost to Follow-up	2 (2.3)	0	0	1 (2.6)
Other[b]	3 (3.5)	0	1 (1.2)	0
Subjects Prematurely Discontinued Study	18 (20.9)	9 (20.9)	8 (9.6)	2 (5.1)
Need for Alternative Antibacterial Agent	0	0	3 (3.6)	1 (2.6)
Lack of Study-qualifying Baseline Culture	15 (17.4)	3 (7.0)	2 (2.4)	1 (2.6)
Developed of Moderate/Severe Renal Impairment	1 (1.2)	0		
Adverse Event or CS Laboratory	0	1 (2.3)	0	0
Withdrew Consent	0	4 (9.3)	0	0
Other[c]	2 (2.3)	1 (2.3)	3 (3.6)	0

CS = clinically significant; n = number of subjects in the specific category Note: All percentages are based on the number of subjects randomized.

[a] Includes subjects who were discontinued from study drug due to lack of a study-qualifying baseline culture but remained on study for completion of safety assessments.

[b] Other reasons for premature withdrawal include "Inclusion Criteria #12" (1 subject) and "Alternative antimicrobial therapy" (2 subjects) in Study CXA-101-03 and "Subject does not require surgical intervention and subject lost to follow-up" in Study CXA-IAI-10-01.

[c] Other reasons for premature discontinuation of study drug include "Subject transferred to VA hospital", "Subject refused further treatment", and "Subject's UTI has completely resolved or improved" in Study CXA-101-03 and "Voluntarily discontinued", "Subject does not require surgical intervention", and "Patient not likely to live and abnormal EKG" in Study CXA-IAI-10-01.

Disposition and Duration of Exposure in the Phase 1 Studies

Across the 9 Phase 1 studies, 305 subjects received study drug, including ceftolozane alone, tazobactam alone, ceftolozane/tazobactam, placebo, or other comparators. The majority of treated subjects completed study drug treatment (98%) and no notable differences were observed between groups in treatment completion rates in any study.
The table below shows the exposure of subjects in the Phase 1 studies.
Ceftolozane was administered as a single agent to 70 subjects in the Phase 1 studies; 42 subjects received ceftolozane as a single dose up to 2 g and 28 subjects received multiple daily doses of ceftolozane up to 3 g for up to 10 days. A total of 179 subjects were exposed to ceftolozane/tazobactam in the Phase 1 studies; 106 subjects received single doses up to 4.5 g and 73 subjects received multiple daily doses up to 9 g for up to 10 days.

Table 49: Subject Disposition in the Phase 1 Studies (Safety Population)

Study	**Treatment Arm**		**Subject Disposition**		
			Enrolled n (%)	**Treated n (%)**	**Completed n (%)**
CXA-101-01	**Total**		**64**	**64**	**64**
Part 1 (SD)	Ceftolozane 250 mg		6	6	6
	Ceftolozane 500 mg		6	6	6
	Ceftolozane 1 g		6	6	6
	Ceftolozane 1.5 g		6	6	6
	Ceftolozane 2 g		6	6	6
	Placebo		10	10	10
Part 2 (MD × 10 days)	Ceftolozane 500 mg q8h		6	6	6
	Ceftolozane 1 g q8h		6	6	6
	Ceftolozane 1.5 g q12h		6	6	6
	Placebo		6	6	6
CXA-201-01	**Total**		**58**	**58**	**57**
Part 1 (SD)	Cohort 1[a]		6	6	6
	Cohort 2[a]		6	6	6
	Cohort 3[a]		6	6	6
Part 2 (MD × 10 days)	Cohort 4	Ceftolozane 1g q8h	5	5	5
		Tazobactam 500 mg q8h	5	5	5

		Ceftolozane/tazobactam 1.5 g q8h	10	10	10
	Cohort 5	Ceftolozane 1.5 g q12h	5	5	5
		Tazobactam 750 mg q12h	5	5	4
		Ceftolozane/tazobactam 2.25 g q12h	10	10	10
CXA-MD-11-07 (MD × 10 days)	**Total**		**16**	**16**	**15**
	Ceftolozane/tazobactam 1.5 g q8h		4	4	4
	Ceftolozane/tazobactam 3 g q8h		8	8	7
	Placebo		4	4	4

Table 50: Subject Disposition in the Phase 1 Studies (Safety Population) (Continued)

Study	Treatment Arm	Subject Disposition		
		Enrolled n (%)	Treated n (%)	Completed n (%)
CXA-ELF-10-03 (3 doses)	**Total**	**51**	**51**	**50**
	Ceftolozane/tazobactam 1.5 g q8h	25	25	25
	Piperacillin/tazobactam 4.5 g q6h	26	26	25
CXA-	**Total**[b]	**16**	**16**	**16**
CXA-	**Total**[c]	**52**	**52**	**50**
CXA-101-02 (SD)	**Total**[d]	**12**	**12**	**12**
	Mild Renal Impairment	6	6	6
	Normal Renal Function	6	6	6
CXA-201-02 (SD)	**Total**[e]	**24**	**24**	**24**
	Mild Renal Impairment	6	6	6
	Moderate Renal Impairment	7	7	7
	Normal Renal Function	11	11	11
CXA-REN-11-01	**Total**[f]	**12**	**12**	**12**
	Severe Renal Impairment	6	6	6
	ESRD on HD Ceftolozane/tazobactam	6	6	6

ESRD = end stage renal disease; HD = hemodialysis; MD = multiple dose; N = number of subjects; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours; SD = single dose.

[a] Subjects in Part 1 of Study CXA-201-01 received single doses of ceftolozane, tazobactam, and ceftolozane/tazobactam at doses of 500, 250 and 750 mg, respectively (Cohort 1), 1000, 500, and 1500 mg, respectively (Cohort 2), or 2000, 1000, and 3000 mg, respectively (Cohort 3).

[b] Subjects in Study CXA-DDI-12-10 received furosemide, midazolam and caffeine, ceftolozane/tazobactam 1.5 g, furosemide with ceftolozane/tazobactam 1.5 g, midazolam and caffeine with ceftolozane/tazobactam 1.5 g during 5 separate dosing periods.
[c] Subjects in Study CXA-QT-10-02 received single doses of ceftolozane/tazobactam 1.5 and 4.5 g, moxifloxacin 400 mg, and placebo in 1 of 4 dosing sequences.
[d] All subjects in Study CXA-101-02 received a single dose of ceftolozane 1 g.
[e] All subjects in Study CXA-201-02 received a single dose of ceftolozane/tazobactam 1.5 g.
[f] Subjects in Study CXA-REN-11-01 received ceftolozane/tazobactam 750 mg as a single dose (severe renal impairment group) or 2 single doses on Days 1 and 4 (ESRD on HD group). Source: ISS

7.2.2 Explorations for Dose Response

There were no exposure-response data generated. All efficacy data were generated using the same dosing regimen.

7.2.3 Special Animal and/or In Vitro Testing

The applicant conducted adequate non-clinical and clinical studies in pharmacology, pharmacokinetics and toxicology. Please refer to Section 4.3 Preclinical pharmacology/toxicology for additional information.

7.2.4 Routine Clinical Testing

The Applicant conducted adequate routine clinical testing during the Phase 2 and 3 trials. There was consistency in the reporting of adverse events between verbatim and preferred terms.

7.2.5 Metabolic, Clearance, and Interaction Workup

Clinical studies have demonstrated the pharmacokinetics (PK) of ceftolozane/tazobactam is linear, has a relatively short terminal elimination half-life ($t_{½}$, approximately 2 to 3 hours and 1 hour for ceftolozane and tazobactam, respectively), and has low protein binding (approximately 16% to 21%). Ceftolozane undergoes minimal metabolism following IV administration in humans with the majority (>90%) of administered drug excreted unchanged in the urine, and is not a substrate for hepatic cytochrome P450 (CYP450) enzymes. Tazobactam and its M1 metabolite are eliminated primarily through glomerular filtration and tubular secretion with >80% as unchanged drug. Tazobactam and its metabolite are not metabolized by CYPs.

Because both ceftolozane and tazobactam are primarily excreted by the kidney via glomerular filtration, the potential for drug-drug interactions is likely limited to drugs excreted by tubular secretion or glomerular filtration. For more details, please refer to Dr. Ryan Owen's review of clinical pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Specific AEs that are associated with the cephalosporin class of drugs, including anaphylaxis, pseudomembranous colitis, hemolytic disorders, thrombophlebitis, and acute renal failure were evaluated and summarized by treatment arm. For more details refer to Section 7.3.

7.3 Major Safety Results

Overall incidence

The overall incidence of TEAEs, SAEs, discontinuation of study drug due to AEs and deaths for the pooled phase 3 studies is summarized in the table below. The overall incidence is similar between ceftolozane/tazobactam and comparators. Overall, in the integrated Phase 3 studies, 397 of 1015 (39%) subjects who received ceftolozane/tazobactam experienced TEAEs. The overall incidence of TEAEs among subjects who received ceftolozane/tazobactam was similar to that in the comparator treatment arm (396 of 1032 subjects; 38%). Overall, the incidence of SAEs in the Phase 3 cUTI and cIAI studies was similar in the ceftolozane/tazobactam treatment arm (54 subjects, 5.3%) and the comparator treatment arm (54 subjects, 5.2%). The incidence of SAEs in subjects with cUTI (3%) relative to subjects with cIAI (8%) was consistent with the more severe nature of the cIAI indication, which involves surgical procedures. Most SAEs were assessed as unrelated to study drug and the incidence of SAEs related to study drug was low and balanced between treatment arms. Overall there was a low incidence of treatment discontinuations due to AEs (approximately 1% to 2%) in both indications, which was balanced between the treatment arms.

Table 51: Overall Summary of Treatment-emergent Adverse Events in the Integrated Phase 3 cUTI and cIAI Studies (Safety Population)

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

Any Treatment Related SAE	2 (0.4)	0	1 (0.2)	1 (0.2)	3 (0.3)	1 (0.1)
Any Treatment Related TEAE leading to Discontinuation of Study Drug	3 (0.6)	6 (1.1)	3 (0.6)	4 (0.8)	6 (0.6)	10 (1.0)
Any Treatment Related TEAE Resulting in Death	0	0	0	0	0	0

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; n = number of subjects in the specific category; N = number of subjects in the Safety population; SAE = serious adverse event; TEAE treatment-emergent adverse event. Source: ISS/Section 2.1 Table 6

In the integrated phase 3 trials, gastrointestinal events were the most frequently reported types of TEAEs. The 5 TEAEs with the highest incidence in the integrated phase 3 studies in the ceftolozane/tazobactam with or without metronidazole (N=1015) vs. all comparators (N=1032) were nausea (5.4% vs 3.7%), headache (4.2 vs 3.4% in all comparators), diarrhea (3.9% vs. 4.7%), pyrexia (3.3 vs 2.4% in all comparators), and constipation (3% vs 2.3%).

Adverse events terms suggesting pseudomembranous colitis were presented by the applicant by MedDRA preferred term across the integrated Phase 3 studies. There were a total of 4 subjects in all ceftolozane/tazobactam treated subjects (4/1015 or 0.4%) and 3 in all comparators arms (3/1032 or 0.3%). The preferred terms included *C. difficile* colitis, pseudomembranous colitis, and clostridial infection. Pseudomembranous colitis was reported in 3 (0.6%) subjects in the ceftolozane/tazobactam arm of the cUTI indication and in 3 (0.6%) subjects of the cIAI indication. One subject in the cIAI indication was reported as an SAE of *Clostridium difficile* colitis, with favorable outcome. All these events resolved with treatment.

Direct Coombs tests were assessed at baseline and at EOT. Two subjects in the ceftolozane/tazobactam arms (1 subject per indication) seroconverted from negative to positive. There were no other laboratory abnormalities associated with the seroconversions and no clinical findings suggestive of hemolytic anemia.

The incidence of phlebitis and thrombophlebitis was low and similar in the ceftolozane/tazobactam arms (8/105 or 0.8%) and comparator arms (11/1032 or 1.1%). However, deep vein thromboses (portal vein thrombosis, deep venous thrombosis, pelvic vein thrombosis) were observed in 4 subjects in the ceftolozane/tazobactam arm (in the cIAI indication only) and in 0 in the meropenem arm. Two of these subjects were reported as having SAEs. One subject in the end stage renal disease cohort of the CXA-REN-11-01 study developed thrombosis of the arteriovenous fistula 4 days after administration of the second dose of 750 mg of ceftolozane/tazobactam, which required hospitalization, heparinization and catheter replacement. This was reported as an SAE.

Any adverse event of renal failure was reported in 11/1015 (1.1%) and 8/1032 (0.8%) subjects in the comparator arms across the phase 3 studies. The terms included renal impairment, oliguria, renal failure acute, prerenal failure acute, azotemia, anuria, dialysis and continuous hemofiltration. The standardized MedDRA query for anaphylaxis terms was performed and two subjects were identified (2 in the ceftolozane/tazobactam arm and 1 in the meropenem arm). One subject in the ceftolozane/tazobactam arm of the cIAI indication, subject 1008-4023-006, a 58 year old female with gastric/duodenal perforation who had hypotension after surgery, and on day 2 presented with pruritus and rash with edema. The subject was receiving opiates and analgesics concomitantly. The events resolved and therapy was administered for 6 days, there was no discontinuation of therapy because of these events. The other subject in the ceftolozane/tazobactam arm identified by the MedDRA query was subject 1009-5412-001, a 59 year old female with a history of asthma and ischemic heart disease who died from sudden death after completing an 11-day course of ceftolozane/tazobactam plus metronidazole. The subject had tolerated the infusions during the course of treatment and the acute shortness of breath and sudden death were not temporally associated with study drug. Severe asthma and other events, such as pulmonary embolism and acute myocardial infarction, are possible causes of death. No autopsy was done. The subject in the meropenem arm, subject 1008-4129-008, was identified by the MedDRA query under the term "circulatory collapse" and was a 63 year old female with diffuse peritonitis who died from worsening infection. The circulatory collapse was likely one of the manifestations of sepsis.

Overview of Adverse Events in cUTI study

Approximately 35% of subjects in each arm experienced at least one treatment emergent adverse event. The proportion of subjects who experienced at least one serious adverse event or who discontinued the drug due to an adverse event was similar in the two treatment arms.

Pyelonephritis as a MedDRA was coded more frequently in the levofloxacin arm. Adding the terms pyelonephritis, pyelonephritis acute or pyelonephritis emphysematous, yields a total of 11 patients in the levofloxacin arm compared to no codes of pyelonephritis in the ceftolozane arm. These cases were treatment failures and reflected efficacy failure in the setting of levofloxacin resistance. UTIs as MedDRA term were coded at a similar frequency in the two treatment arms, but adding the events coded as *E. coli* UTI, Enterococcal UTI, UTI bacterial, bacteriuria and cystitis, the frequency of events that indicate urinary infection increases to 19 (3.6%) in the ceftolozane/tazobactam arm and to 12 (2.2%) in the levofloxacin arm. The table shows MedDRA terms as reported in at least 1% of patients, without lumping of terms.

Table 52: Treatment Emergent Adverse Events Occurring in ≥1% of Subjects in Either Treatment Arm – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 533	**Levofloxacin N = 535**
Subjects with any TEAE	185 (34.7%)	184 (34.4%)

Gastrointestinal Disorders	63 (11.8%)	61 (11.4%)
Abdominal pain upper	7 (1.3%)	6 (1.1%)
Constipation	21 (3.9%)	17 (31.8%)
Diarrhea	10 (1.9%)	23 (4.3%)
Nausea	15 (2.8%)	9 (1.7%)
Vomiting	6 (1.1%)	6 (1.1%)
General Disorders	27 (5.1%)	21 (3.9%)
Pyrexia	8 (1.5%)	4 (0.7%)
Infections and Infestations	38 (7.1%)	41 (7.7%)
UTI	9 (1.7%)	9 (1.7%)
Pyelonephritis	0	7 (1.3%)
Investigations	12 (2.2%)	13 (2.4%)
ALT increased	9 (1.7%)	5 (0.9%)
AST increased	9 (1.7%)	5 (0.9%)
Musculoskeletal Disorders	9 (1.7%)	15 (2.8%)
Myalgia	6 (1.1%)	4 (0.7%)
Arthralgia	0	6 (1.1%)
Nervous System Disorders	41 (7.7%)	33 (6.2%)
Dizziness	6 (1.1%)	1 (0.2%)
Headache	31 (5.8%)	26 (4.9%)
Psychiatric Disorders	11 (2.1%)	18 (3.4%)
Insomnia	7 (1.3%)	14 (2.6%)
Vascular Disorders	22 (6.1%)	19 (3.6%)
Hypertension	16 (3.0%)	9 (1.7%)

Overview of Adverse Events in cIAI phase 3 study

A total of 212 out of 482 subjects (44%) experienced at least one TEAE in the ceftolozane/tazobactam + metronidazole arm. In the meropenem arm, 213 of 497 subjects experienced a TEAE (42.9%). Gastrointestinal events were the most frequently reported types of TEAEs. The TEAEs with the highest incidence in the ceftolozane/tazobactam plus metronidazole treatment arm were nausea (8.3%), diarrhea (6.2%), pyrexia (5.2%), insomnia (3.5%), and vomiting (3.3%). Similarly, the TEAEs with the highest incidence in the meropenem treatment arm were nausea (6.2%), diarrhea (5.1%), pyrexia (4.1%), vomiting (4.0%), and insomnia (2.2%).

Table 53: AEs > or = 1% in any treatment arm- cIAI Phase 3 trial - Safety Population

	Ceftolozane/Tazobactam N = 482	**Meropenem N = 497**
Subjects with any TEAE	**212 (44%)**	**213 (42.9%)**
Gastrointestinal Disorders	**100 (20.7%)**	**84 (16.9%)**
Nausea	40 (8.3%)	29 (5.8%)
Diarrhea	30 (6.2%)	25 (5%)

Pyrexia	26 (5.2%)	20 (4%)
Vomiting	16 (3.3%)	20 (4.0%)
General Disorders	**50 (10.4%)**	**43 (8.7%)**
Peripheral edema	9 (1.9%)	4 (0.8%)
Infusion site reactions	4 (0.8%)	10 (2%)
Cardiac disorders	**21 (4.4%)**	**16 (3.2%)**
Atrial fibrillation	6 (1.24%)	3 (0.6%)
Tachycardia	7 (1.45%)	10 (2.0%)
Blood and lymphatic system disorders	**19 (3.9%)**	**16 (3.0%)**
Anemia	6 (1.2%)	4 (0.8%)
Thrombocytosis	9 (1.9%)	5 (1.0%)
Infections and Infestations	**34 (7.1%)**	**50 (10.1%)**
Abdominal abscess and infections/abd. sepsis	8 (1.6%)	13 (2.6%)
Pneumonia	6 (1.2%)	6 (1.2%)
Urinary tract infection	6 (1.2%)	2 (0.4%)
Injuries, poisoning, procedures	**26 (5.4%)**	**32 (6.4%)**
Anemia post-operative	10 (2.0%)	8 (1.6%)
Seroma	6 (1.2%)	7 (1.4%)
Wound evisceration, dehiscence or secretion	10 (2.0%)	8 (1.6%)
Investigations	**23 (4.8%)**	**21 (4.2%)**
ALT increased	7 (1.5%)	5 (1%)
AST increased	5 (1%)	3 (0.6%)
Gamma GT	3 (0.6%)	5 (1%)
Metabolism and nutrition disorders	**39 (8.1%)**	**34 (6.8%)**
Hyperglycemia	6 (1.2%)	3 (0.6%)
Hypoalbuminemia	7 (1.5%)	8 (1.6%)
Hypomagnesemia	6 (1.2%)	5 (1%)
Hypokalemia	14 (2.9%)	8 (1.6%)
Hypophosphatemia	5 (1%)	3 (0.6%)
Hypocalcemia	4 (0.8%)	9 (1.8%)
Nervous System Disorders	**28 (5.8%)**	**21 (4.2%)**
Headache	12 (2.5%)	9 (1.8%)
Dizziness	4 (0.8%)	5 (1%)
Psychiatric Disorders	**34 (7.1%)**	**28 (5.6%)**
Insomnia	17 (3.5%)	11 (2.2%)
Anxiety	9 (1.9%)	7 (1.4%)
Renal and Urinary Disorders	**19 (3.9%)**	**16 (3.2%)**
Renal Impairment	7 (1.4%)	3 (0.6%)
Dysuria	5 (1%)	2 (0.4%)
Respiratory and thoracic disorders	**32 (6.6%)**	**36 (7.2%)**
Pleural effusion	9 (1.9%)	7 (1.4%)

Pleurisy/pleuritic pain	5 (1%)	1 (0.2%)
Cough	1 (0.2%)	6 (1.2%)
Dyspnea	4 (0.8%)	6 (1.2%)
Skin and subcutaneous tissue	**14 (2.9%)**	**15 (3%)**
Rash	8 (1.6%)	7 (1.4%)
Vascular disorders	**25 (5.2%)**	**23 (4.6%)**
Hypertension	10 (2.0%)	10 (2.0%)
Hypotension	8 (1.6%)	0 (0%)
Thrombosis or thrombophlebitis	6 (1.2%)	0 (0)
Phlebitis, phlebitis superficial	3 (0.6%)	7 (1.4%)

Overview of safety in the Phase 2 studies

Phase 2 cIAI study

A total of 34 of 82 (41%) and 16 of 39 (41%) subjects in the ceftolozane/tazobactam plus metronidazole and meropenem arm, respectively, reported at least one TEAE. The most commonly reported TEAEs were pyrexia (14.7% and 10.3% in the ceftolozane/tazobactam and meropenem groups, respectively) nausea (6.1% and 10.3% in the ceftolozane/tazobactam and meropenem groups, respectively) and vomiting (6% and 7.7% in the ceftolozane/tazobactam and meropenem groups, respectively). Other TEAEs that occurred at a rate of 3% or greater in the ceftolozane/tazobactam plus metronidazole group and were higher than in the comparator included anemia (7.2% vs 2.6%) post-operative anemia (3.6% vs 2.6%), ileus (3.6% vs 0), hypokalemia (3.6% vs 2.6%) , atelectasis (3.6% 0), and hypertension (6% vs 5.1%).

Three subjects in the ceftolozane/tazobactam group died, all within 30 days of the last dose. The events leading to death were urosepsis, pulmonary embolism, and renal failure with cardiopulmonary arrest. These were possibly related to the underlying infection and predisposing conditions. No deaths were observed in the meropenem arm.
The incidence of SAEs was higher in the ceftolozane/tazobactam group (14 subjects, 17.1%) compared to the meropenem group (2 subjects, 5.1%). Based on clinical assessment, in 5 of the 14 subjects in the ceftolozane/tazobactam group, SAEs were primarily related to clinical failure or relapse and in 6 subjects the events were primarily related to the underlying intraabdominal infection or surgical procedure; vascular and cardiac disorders reported as SAEs in 2 subjects were related to underlying cardiac disease and 1 event of pneumonia was reported 6 days post-treatment.

Two of the SAEs led to treatment discontinuation, both were associated with clinical failures. In the meropenem group the 2 SAEs were related to the underlying intraabdominal infection or surgical procedure and 1 of the SAEs was reported in a subject with a clinical outcome of failure.

Laboratory Evaluations
The most common post-baseline shifts in clinical laboratory parameters were elevated gamma-glutamyl transferase (GGT), aspartate transaminase (AST), and alanine transaminase (ALT). For all 3 parameters, a higher proportion of subjects in the meropenem treatment group had post-baseline shifts of ≥2 toxicity grades than in the CXA-101/tazobactam treatment group (GGT: 34.2% versus 7.0%; AST: 18.9% versus 10.6%; ALT: 21.1% versus 7.0%). Shifts of ≥2 toxicity grades for hemoglobin were reported more often in the ceftolozane/tazobactam group (14.5%) compared to the meropenem group (6.1%); possibly related to complicated surgical procedures in high-risk subjects or the subject's underlying condition.
There were no clinically meaningful differences noted between the treatment groups for changes from baseline in vital signs.

Phase 2 cUTI study

A treatment-emergent AE (TEAE) was defined as an AE that started or worsened at or during the time of or after the first study drug administration through the follow-up visit. (MedDRA v. 12.0)

The most commonly reported TEAEs (i.e., reported in 2 or more of subjects in either treatment group) regardless of relationship to study drug were constipation (9.4% and 4.8% in the ceftolozane and ceftazidime groups, respectively), sleep disorder (7.1% and 4.8%, respectively), nausea (5.9% and 0%, respectively), headache (5.9% and 0%, respectively), diarrhea (3.5% and 7.1%, respectively), insomnia (4.7% and 0%, respectively), pyrexia (3.5% and 2.4%, respectively), infusion site irritation (3.5% and 0%, respectively), abdominal pain (2.4% and 2.4%, respectively), back pain (2.4% and 2.4%, respectively), and infusion site erythema, infusion site extravasation, infusion site swelling, flank pain, urinary tract infection, hypertension, phlebitis, and cough (each 2.4% and 0%, respectively). Two subjects discontinued study drug due to adverse events, including 1 subject in the ceftolozane group whose CrCl decreased to <50 mL/min on Day 3 and 1 subject in the ceftazidime group who was discontinued due to vomiting and diarrhea.

One subject in the CXA101 arm and one subject in the ceftazidime arm discontinued treatment due to an AE. The subject in the CXA101 arm was discontinued on Day 4 due to decrease in CrCl from 51 at baseline to 39, and an increase of Cr from 1.3 at baseline to 1.6. Corresponding levels from the central lab showed a stable Cr at 1.1. The AE was assessed as not drug related. The subject in the ceftazidime arm was discontinued on Day 6 due to vomiting and diarrhea. The narrative states that his symptoms resolved within one day.

There were no deaths during the study. One subject in the CXA-101 arm experienced a SAE. The patient was a 42 year old woman with history of recurrent pyelonephritis and nephrolithiasis. She received 8 days of CXA-101 for *E. coli* pyelonephritis and was assessed as having clinical and microbiologic cure at TOC visit. Nine days after TOC visit, she was admitted with recurrent symptoms of pyelonephritis. The SAE was assessed as not drug related.

Laboratory Evaluations
Toxicity shifts >1 grade for hemoglobin and WBC respectively occurred in 3 and 2 subjects in the CXA-101 arm (3.8%, 3%). No subject had a shift in platelet count or coagulation parameters. This is compared to no subject in the ceftazidime arm with shift in CBC values and 3 subjects with shift in aPTT. No subject in either treatment arm had elevation of AST or ALT to >3xULN on Day 3 or at TOC visit. No subject met the criteria for Hy's rule. There was an imbalance in the incidence of hyperglycemia severity grade shifts observed in the CXA-101 group; the shifts in serum glucose were transient, especially in non-diabetic patients, and serum glucose values were mostly below the upper limit of normal for non-fasting subjects. No unexpected clinically significant changes in vital signs were noted.

7.3.1 Deaths

In the integrated Phase 3 studies, 12 subjects in the ceftolozane/tazobactam treatment arm and 8 subjects in the comparator treatment arm had TEAEs leading to death.
Nineteen of the deaths were in subjects with cIAI (11/482 [2.3%] and 8/497 [1.6%] in the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively). In the phase 2 cIAI study, three deaths occurred in ceftolozane/tazobactam treated subjects. The total of deaths in cIAI studies is 14/564 (2.48%) in the ceftolozane/tazobactam arm and 8/536 (1.49%) in the meropenem arm. The adjusted difference in all-cause mortality is 1.0% (95% CI: -0.9%, 2.8%).

In the cUTI indication, there was 1 death in the ceftolozane/tazobactam treatment arm and no deaths in the levofloxacin treatment arm. The subject died from bladder cancer 38 days after the end of study therapy. The death was assessed as unrelated to study therapy or the underlying cUTI by both the investigator and the applicant.

The narratives and the CRFs of all 23 deaths (15 in the ceftolozane/tazobactam arm and 8 in the comparator arms) in the study were reviewed. A summary of the narratives is presented below, following the general overview of all deaths.

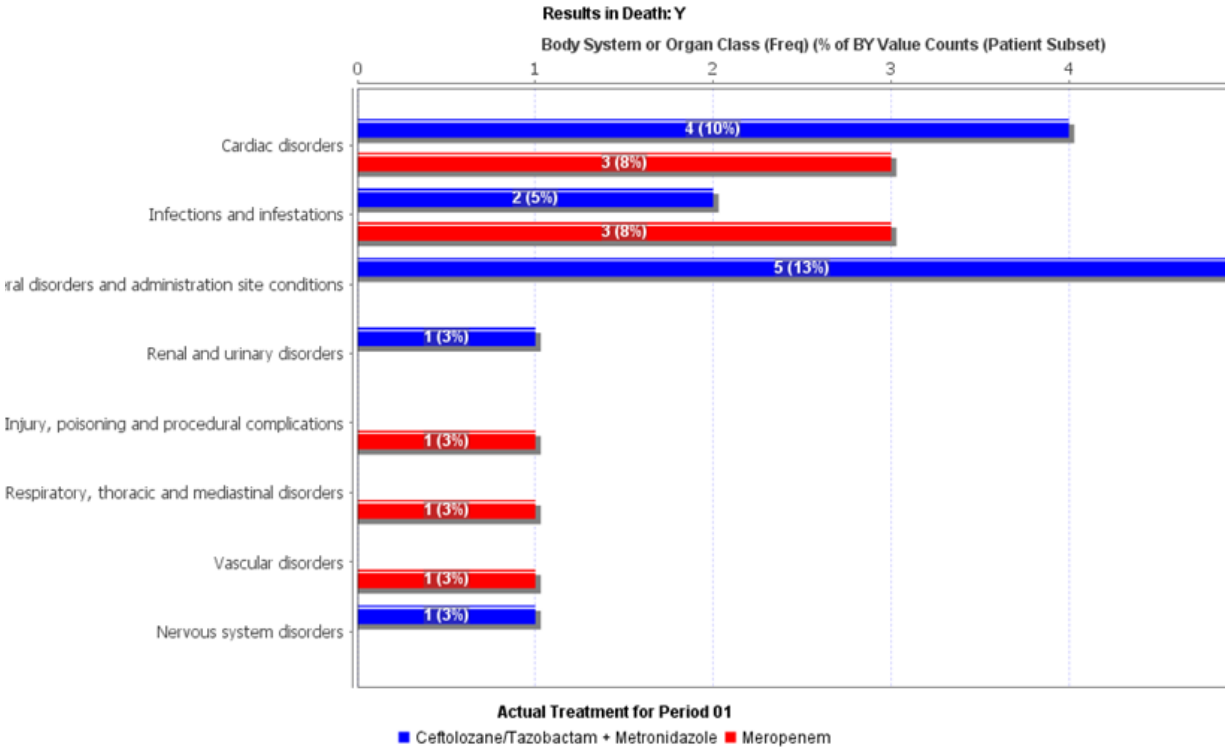
In the cIAI phase 3 study, seven subjects died while on study therapy or within 24 hours of termination of study drug (4 subjects versus 3 subjects in the ceftolozane/tazobactam versus meropenem treatment arms, respectively), while 12 subjects (7 subjects versus 5 subjects in the ceftolozane/tazobactam versus meropenem arms, respectively) died more than 24 hours after the last dose of study drug.. All deaths but 1 occurred within 30 days of study start. One death occurred at study day 32.
None of the deaths were considered by the investigators as related to the study drug, and were attributed to complications of the infection and/or surgery in subjects who had underlying chronic conditions, most commonly cardiovascular and respiratory in nature.

Deaths on the ceftolozane/tazobactam arm were attributed to cardiac failure, cardiac shock or cardiopulmonary failure (3 subjects), myocardial infarction (1 subject), septic shock (1 subject)

or multi-organ failure (MOF; 3 subjects), sudden death (2 subjects), ischemic stroke (1 subject) and renal failure (1 subject). In the meropenem arm, 4 deaths were attributed to cardiovascular events (circulatory collapse or cardiovascular insufficiency, 2 subjects, atrial fibrillation 1 subject, myocardial infarction, 1 subject), one death to pulmonary embolism and 2 deaths to infections (septic shock and graft infection). There were a total of 19 deaths and 22 adverse events with fatal outcome. Three patients (1009-6477-006, 1008-4714-008 and 1009-6276-006) had more than one SAE coded as fatal.

The figure below shows the slight imbalance in deaths for the ceftolozane/tazobactam arm, represented in blue, driven by cardiac events (4 vs 3 events in the meropenem arm) and mainly by general disorders and administration conditions (where 3 multi-organ failures and 2 sudden deaths were classified in the ceftolozane/tazobactam arm, vs 0 in the meropenem arm).

Figure 2: Fatal Adverse Events by System Organ Class



The three subjects with multi-organ failure and the two cases of sudden death are summarized below.

- Subject 1008-4714-008 was an 81-year-old male with ischemic cardiomyopathy and grade III hypertension who was enrolled after prior failure of a colo-colonic anastomosis and a treatment course of ertapenem. He received three days of treatment with ceftolozane/tazobactam plus metronidazole and developed a stroke in the right occipital lobe. Seven days after drug discontinuation he had surgery again for removal of necrotic bowel. He died from multi-organ failure 11 days after study drug discontinuation, from cardiac arrest; both multi-organ failure and cardiac arrest were listed as fatal adverse events. The

subject's age, medical history, development of acute stroke, along with serious surgical complications and an ongoing intra-abdominal sepsis likely contributed to the cardiac arrest. The possible lack of source control cannot be excluded. There was no autopsy.

- Subject 1008-4127-025, a 73-year-old male who was admitted with a transient ischemic attack, completed a course of ceftolozane/tazobactam and on Day 8 presented with fever and abdominal pain. A CT scan revealed multiple abscesses that were drained and grew *Staphylococcus lentus* and *Staphylococcus epidermidis*. Antibacterial treatment was switched to ciprofloxacin on Day 8 and over the next 14 days the patient underwent three laparotomies for multiple colonic perforations and abscesses. The surgical review panel assessed the subject as having had inadequate source control. Lymphoma of the caecum, which led to complications and multiple events of intestinal perforation with sepsis in an elderly subject coupled with inability to control the source of infection are plausible reasons for MOF and death.

- Subject 1009-6276-006, a 60-year-old white male with chronic hypertensive heart disease, alcoholic liver cirrhosis, alcohol-induced chronic pancreatitis, hepatic fibrosis, type 2 diabetes mellitus, hypertension, and chronic active proctitis was enrolled in the study with an abscess in the rectovesical pouch due to spontaneous colon perforation. The baseline abscess culture results were positive for *P. mirabilis, E. cloacae, E. faecalis,* and *S. haemolyticus*. On Day 7 of ceftolozane/tazobactam plus metronidazole therapy, the subject developed chest pain, bradycardia and hypotension without significant EKG findings. On Study Day 10 the subject was discontinued from the study drug and assessed as clinical failure because of wound infection (no cultures were obtained). On the same day he had cardiovascular and respiratory collapse and was intubated. The patient died in the ICU on the next day. An autopsy revealed chronic active proctitis with purulent paraproctitis and purulent pelvic peritonitis, together with renal and hepatic insufficiency. The autopsy also revealed acute hemorrhagic gastroduodenal ulcers; dystrophy of the renal parenchyma; myocardial lesion; acute hyperemia of the lungs, kidneys and spleen; pulmonary and cerebral edema; pulmonary atelectasis; and encephalomalacia of the right occipital lobe. The subject's death appeared to be related to co-morbidities coupled with complications of the underlying infection and lack of treatment effect, resulting in MOF and death. The investigator stated that the subject's death appeared to be related to co-morbidities coupled with complications of the underlying infection and lack of treatment effect, resulting in MOF and death.

- Subject 1009-6275-019, a 79-year-old white male with Grade 3 chronic obstructive pulmonary disease (COPD) was enrolled in the study with a diagnosis of perforated gangrenous cholecystitis and acute diffuse peritonitis. The subject improved and was able to tolerate oral intake following surgery. On Study Day 3, after 4 doses of ceftolozane/tazobactam plus metronidazole, the subject complained of abdominal pain and received intramuscular pethidine (50 mg). Approximately 3 hours later, the subject was found dead with cyanosis of the face and upper part of the body. As no autopsy was performed, the event leading to death could not be determined and was reported as "sudden death". The investigator considered that the death may be attributed to complications from

the underlying intra-abdominal infection and surgical procedure and underlying co-morbidities in an elderly subject.

- Subject No. 1009-5412-001, a 59-year-old white female with a significant medical history of ischemic heart disease, arterial hypertension, uncontrolled bronchial asthma, and dyslipidemia was enrolled in the study with a diagnosis of recurrent incarcerated umbilical hernia, intestinal perforation and necrosis, and peritonitis. The subject completed an 11-day course of therapy with ceftolozane/tazobactam plus metronidazole with complete resolution of all abdominal symptoms except mild abdominal pain. On the same day, the subject complained of respiratory constriction resulting from worsening bronchial asthma, treated with intravenous aminophylline. Approximately 14 hours after the last dose of study drug and without any other reported clinical signs, symptoms or complaints, the subject unexpectedly died. As no autopsy was performed, the event leading to death could not be determined and was reported as "sudden death." The event of sudden death was assessed by the investigator as likely due to the subject's underlying ischemic heart disease and uncontrolled asthma.

Medical Reviewer's comment: *Overall, I agree with the investigators' assessments on these deaths. The subjects' underlying co-morbidities, especially cardiac and respiratory diseases, and old age in most of the cases, could have contributed to these deaths after a major surgical procedure, which is an additional risk factor. A lack of efficacy of the drug could have likely contributed to the death, at least in two of the cases of multi-organ failure and in one of the sudden deaths; however, the lack of source control after the surgical procedure, the uncertainty about the time of evolution of the infection before the diagnosis was made and additional co-morbidities are confounding factors that make the assessment of causality of these deaths difficult. All these deaths were assessed as treatment failure or indeterminate, which were counted as treatment failure in the primary analysis of efficacy.*

Serious Adverse Events with fatal outcomes by treatment arm in the phase 3 cIAI study

The table below shows the type and number of patients who had events with a fatal outcome.

Table 54: Serious Adverse Events with Fatal Outcomes

Serious Adverse Event	**Ceftolozane/Tazobactam + Metronidazole N=11**	**Meropenem N=8**
Multi-organ failure	3 (27.27%)	0 (0.00%)
Sudden death	2 (18.18%)	0 (0.00%)
Cardiogenic shock	1 (9.09%)	0 (0.00%)
Cardiopulmonary failure	1 (9.09%)	0 (0.00%)
Intestinal perforation	1 (9.09%)	0 (0.00%)
Ischaemic stroke	1 (9.09%)	0 (0.00%)
Large intestine perforation	1 (9.09%)	0 (0.00%)
Lung infection pseudomonal	1 (9.09%)	0 (0.00%)
Cardiac failure	1 (9.09%)	0 (0.00%)
Myocardial infarction	1 (9.09%)	1 (14.29%)
Pneumonia staphylococcal	1 (9.09%)	0 (0.00%)
Rectal perforation	1 (9.09%)	0 (0.00%)
Renal failure acute	1 (9.09%)	0 (0.00%)
Septic shock	1 (9.09%)	2 (28.57%)
Staphylococcal bacteraemia	1 (9.09%)	0 (0.00%)
Atrial fibrillation	0 (0.00%)	1(14.29%)
Acute respiratory distress syndrome	1 (9.09%)	0 (0.00%)
Wound evisceration	1 (9.09%)	0 (0.00%)
Circulatory collapse	0 (0.00%)	1 (14.29%)
Pulmonary embolism	0 (0.00%)	1 (14.29%)
Road traffic accident	0 (0.00%)	1 (14.29%)
Cardiovascular insufficiency	0 (0.00%)	1 (14.29%)

Multi-organ failure (3 cases), sudden death (2 cases) and intestinal and rectal perforations (3 cases) were observed only in the ceftolozane/tazobactam arm. A summary of these five cases' narratives is presented above. Two subjects in the meropenem arm and one subject in the ceftolozane/tazobactam arm died from septic shock as a consequence of worsening intra-abdominal infection.

Cardiovascular events (cardiac failure, cardiac shock, circulatory collapse, cardiovascular insufficiency and myocardial infarction) were fatal in 4 subjects in the ceftolozane/tazobactam plus metronidazole arm and in 3 of subjects in the meropenem arm. Two cases of pneumonia, one by *Pseudomonas spp*. and one by *Staphylococcus aureus* and one case of staphylococcal

bacteremia were fatal in the ceftolozane/tazobactam plus metronidazole arm versus 0 in the meropenem arm.

Summary narratives of the deaths in the ceftolozane/tazobactam arm are presented and commented on below.

- Subject 1008-4020-013, was an 81 year old female from the United States with history of hypertension, aortic arteriosclerosis and mitral valve incompetence, who was randomized into the study after having a laparotomy for perforated diverticulitis and multiple abscesses. Three days prior to randomization she had had an episode of rapid atrial fibrillation, treated with IV diltiazem. On study day 3 she developed pulmonary infiltrates that progressed and on study day 4 was diagnosed with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. On study day 7 she was diagnosed with pneumonia with a chest x-ray showing progressive infiltrates and marked leukocytosis (37.6K/mL). Ceftolozane/tazobactam was then discontinued and rifampin and vancomycin started. The subject had another positive respiratory culture 18 days after the last dose of study therapy, which grew *Pseudomonas aeruginosa*, which was treated with IV piperacillin/tazobactam. The subject died of *Pseudomonas* pneumonia 23 days after the last dose of study therapy. The event was considered a ventilator associated pneumonia and not related to the study drug.
    - *MO comment: I agree with the investigator, the clinical, laboratory and chest x-ray findings suggest that this death is due to ventilator-associated pneumonia caused by Pseudomonas aeruginosa, which was diagnosed on study day 7 and prompted study drug discontinuation. The subject received alternative antibacterial therapy for several days before death and died 23 days after the last dose of study drug therapy.*
- 1009-9003-001 was an 80 year old female from Croatia with a history of coronary artery disease with previous coronary artery bypass, and hypertension, who was enrolled after a laparotomy which revealed a perforated rectosigmoid diverticulitis with multiple abscesses, for which she had a rectosigmoidectomy with a colostomy. Her cultures grew *Escherichia coli*, *Streptococcus viridans* and *Bacteroides* species. On day 2 of ceftolozane/tazobactam plus metronidazole, the subject experienced intermittent episodes of respiratory failure that required intubation and mechanical ventilation. She had sudden tachycardia, cyanosis of the extremities, hypotension, a small pleural effusion, and on study day 3 developed ventricular fibrillation and died. The event cardiopulmonary failure was considered related to peritonitis and sepsis, which in this elderly subject with ischemic heart disease was fatal.
    - *MO comment: the underlying infection and potentially lack of source control appear to have played a main role in this subject's death. A lack of efficacy of the study drug cannot be ruled out, although the treatment exposure was brief (2 days) to make a definitive conclusion.*
- 1009-6376-009 was a 76 year old female from Lithuania with a history of hypertension, myocardial ischemia and ischemic stroke, who was randomized after a laparoscopic appendectomy with diffuse peritonitis. On day 4 of ceftolozane/tazobactam plus

metronidazole she did not have clinical improvement of her intra-abdominal disease. On day 5 the subject started treatment with warfarin for thrombosis prophylaxis and the same day she had shortness of breath. On day 6 of study medication, she received dexamethasone for shortness of breath and had paroxysmal supraventricular tachycardia. No cardiac enzymes were tested. She was treated with furosemide and metoprolol. On day 7 she developed an undetermined arrhythmia, hypotension and died. The event was reported by the investigator as cardiogenic shock caused by cardiac arrhythmia, related to ischemic heart disease, not related to study therapy. No EOT assessment of clinical response was made.

- *MO comment: the sudden shortness of breath, accompanied with supraventricular tachycardia in this post-surgical patient with history of ischemic cardiovascular disease makes the diagnosis of pulmonary embolism a likely possibility, among others, such and acute myocardial infarction with heart failure or as septic shock. There are insufficient records regarding the clinical presentation. No work-up for pulmonary embolism was done and electrocardiogram and cardiac enzymes results were not provided in the CRF or narrative, therefore, it is not possible to determine with certainty the cause of death. However, I agree with the investigator in that it is unlikely related to study drug, although a potential lack of efficacy cannot be ruled out, since there is temporal association and no clinical signs of intra-abdominal infection improvement after 7 days of study drug exposure.*

- 1009-4811-003 was a 74 year old female from Serbia, with history of hypertension, type II diabetes and chronic obstructive pulmonary disease, who was randomized to ceftolozane/tazobactam plus metronidazole after a laparotomy for a perforated gangrenous cholecystitis. She completed 6 days of therapy and was discharged home one day after the EOT visit. A week after being discharged, the patient had chest pain and collapsed at home and died from an unconfirmed myocardial infarction. The death was 17 days after having received the last dose of study therapy, and before the TOC visit. The death was attributed to the patient's underlying heart and respiratory conditions and age.
  - *MO comment: the patient died while at home before the TOC visit. No information is available on the events prior to the death and no clinical assessment was done before, during or after the subject's death. A myocardial infarction with acute heart failure is a possibility among others, such as pulmonary embolism.*
- 1009-4206-003 was a 55 year old female from Argentina with history of invasive cervical cancer resection who was randomized to ceftolozane/tazobactam plus metronidazole after an exploratory laparoscopy that diagnosed diffuse peritonitis and a hard necrotic tumor (size unknown) in the uterine body. The uterine body tumor was biopsied and histopathology confirmed uterine cancer. The subject underwent a transverse colostomy and drainage of purulent liquid from the abdominal cavity. The rectal perforation was repaired with no resection. The subject completed 7 days of ceftolozane/tazobactam plus metronidazole. On study day 7, the subject experienced acute right flank pain. An abdominal evisceration was suspected, with persistent cough as a possible cause. An

abdominal ultrasound revealed a distended gallbladder, bilateral kidney pelvic calyceal dilation, and a small amount of fluid in the left flank. A new laparotomy was performed where an abdominal evisceration was confirmed. The investigator assessed the outcome as clinical failure, and the wound evisceration was reported as an SAE. On that same day, ceftolozane/tazobactam plus metronidazole were discontinued and vancomycin and imipenem were started. The subject had another wound evisceration 15 days after the last dose of study therapy and was admitted for wound repair. She developed renal failure after wound repair (18 days after the last dose of ceftolozane/tazobactam plus metronidazole). The subject died 25 days after the last dose of study therapy. The investigator attributed the acute renal failure to outflow obstruction probably related to the cervical cancer. A urinary catheter was not placed and the subject refused hemodialysis treatment. The renal failure did not have a temporal or causal relationship to the study drug, and was related to obstructive nephropathy.

- *MO comment: This death was likely caused by surgical complications (wound evisceration requiring multiple repairs) and by the underlying cervical cancer causing obstructive renal failure. The death does not appear temporally or causally associated to the study drug. The subject had received alternative antibacterial treatment for 7 days after completing ceftolozane/tazobactam therapy and prior to developing renal failure.*

- 1008-4127-002 was a 66 year old male from Slovakia with a history of colon cancer, hypertension and stroke with aphasia, who was randomized to ceftolozane/tazobactam plus metronidazole after being diagnosed with peritonitis with colon as the source. A CT scan had revealed an abscess below the cecum, she had a laparotomy where drainage was performed. The subject received 9 days of therapy with ceftolozane/tazobactam plus metronidazole. The subject was receiving low molecular weight heparin for thromboembolism prophylaxis since day 1. On study day 9 in the morning, the subject's blood pressure was 112/72 mmHg, oxygen saturation was 93%. In the afternoon, the subject suddenly fell unwell (no symptoms description and no vital signs were recorded in the CRF or reported in the narrative). The investigator considered the event to be cardiac failure (heart failure), not related to study drug, and considered it to be related to suspected pulmonary embolism.
  - *M.O. comment: the acute nature of the event in this subject with risk factors for thromboembolic disease (ischemic stroke, hypertension, post-surgical status) makes pulmonary embolism a likely cause, among others, such as acute myocardial infarction with heart failure. However, the lack of detailed information about this case makes the differential diagnosis difficult. No autopsy was performed. The underlying conditions and ongoing infection may have contributed to the subject's death. I agree that the event is probably not related to the study drug.*

Deaths in the meropenem arm

There were a total of 8 deaths in the meropenem arm, and none of them were considered related to study drug. A summary of the narratives is presented below.

- Subject 1009-6477-008 was an 81 year old female from Israel with history of hypertension, ischemic heart disease and dyslipidemia, who was randomized to meropenem after a colectomy and ileostomy for an intestinal perforation. She developed acute heart failure on Day 9 and a myocardial infarction was confirmed. Pulmonary embolism (PE) was a possibility; however, the CT scan did not show suggestive signs of PE.
- Subject 1009-6477-006 was a 69 year old female from Israel with a history of hypertension, ischemic heart disease and peripheral vascular disease who was randomized to meropenem after a cholecystectomy for gangrenous acute cholecystitis. She received 6 days of meropenem and was discharged with no systemic or abdominal signs or symptoms of infection. Ten days after the last dose of study therapy she experienced infection of the graft in her left leg (where she had had an amputation due to peripheral vascular disease). The subject developed fever and sepsis due to this infection. She also had atrial fibrillation. The graft infection and atrial fibrillation were reported as SAEs. The subject died 24 days after the last dose of study therapy, from uncontrolled atrial fibrillation. It is plausible that the known impaired arterial blood flow to the leg was a contributing factor to the infected graft. Hypertension, advanced vascular disease and sepsis are known contributors to the pathogenesis of atrial fibrillation.
- Subject 1009-4129-008 was a 63 year old female from Slovakia with a history of rectal cancer, rectal resection 10 days before randomization and hypertension. The subject was enrolled after a second laparotomy to repair an anastomotic leak. She received 10 days of treatment with meropenem. She had complete resolution of the intra-abdominal infection. Three days after the last dose of study therapy, the subject fell, and she was unconscious and hypotensive. The circulatory collapse was interpreted by the investigator as probably caused by a pulmonary embolism and not to study drug or to the underlying infection, since she had had a successful outcome from that.
- Subject 1008-6652-015 was a 58 year old male from Latvia with a history of hypertension and diabetes mellitus, who was randomized to meropenem after a laparotomy for removal of a gangrenous cholecystitis with an abscess in the liver bed. The subject received 6 days of therapy, with complete resolution of signs and symptoms, had an outcome of cure and was discharged home. The subject was involved in a car accident 18 days after last dose of study therapy and died from trauma to the head. The death was not related to the study drug or underlying illness.
- Subject 1008-4720-001 was a 58 year old from Romania with a history of hypertension who was randomized to meropenem after a laparotomy and segmental enterectomy due to bowel necrosis and diffuse peritonitis. The investigator reported that the necrosis was due to a mesenteric arterial obstruction. The subject had received 8 days of therapy when she had acute respiratory failure requiring intubation and mechanical ventilation. On day 9 she developed fever, marked leukocytosis and hemodynamic instability. Meropenem was

discontinued and imipenem was started. The subject died on study day 12. The event septic shock was reported as the cause of death.

- Subject 1008-8108-001 was an 88 year old female from the Russian Federation with asthma, hypertension, type II diabetes and ischemic heart disease, who was randomized to meropenem after a laparotomy and colostomy for perforated diverticulitis and diffuse peritonitis. The subject received 10 days of meropenem treatment and, on day 10, she presented wheezing and other clinical evidence suggestive of pulmonary embolism. She died 4 days after the last dose of study drug therapy. An autopsy was performed and revealed that the cause of death was massive thromboembolism of the right pulmonary artery and severe chronic cardiac failure.
- Subject 1008-7404-006 was an 80 year old female from Colombia with a history of hypertension and anemia and gastric bleeding who was randomized to meropenem after a laparotomy for multiple intestinal perforations for which a jejunal resection was done. The subject received 4 days of meropenem. On day 3, the subject was drowsy but responsive and tachypneic. On day 4 she became unresponsive due to severe metabolic acidosis due to abdominal sepsis. She had hemodynamic instability and died on the same day. The investigator considered the sepsis related to the intra-abdominal infection.
- Subject 1008-8106-004 was a 41 year old from the Russian Federation with history of alcoholism, chronic pancreatitis and esophageal perforation who was randomized to meropenem after a laparotomy to treat a duodenal perforation with a Billroth type 1 gastrectomy. On day 2 of meropenem he became hypotensive and developed cardiovascular insufficiency with severe bradycardia. The subject died that same day. He had received two doses of meropenem at the time of death. An autopsy was performed and revealed diffuse peritonitis, pulmonary edema and "shock kidney." The cause of death was reported as acute cardiovascular insufficiency caused by esophageal perforation.

Table 55: Deaths in cIAI (Phase 2 and 3) and cUTI studies (Phase 3) –Reviewer's table

Actual Treatment	Unique Subject Identifier	Age/Sex/ Race	Dictionary-Derived Term	Study Day of Death	(Days) Exposure to Treatment	APACHE Score at Baseline	Start of AE Study Day of	End of AE Study Day of	to Treatment Day of Last Exposure	of Study Drug Discontinuation Reason
Phase 3 cIAI study										
Meropenem	1008-4129-008	63/F/W	Circulatory collapse	13	8.4	5	13	13	10	
	1008-4720-	58/M/W	Septic shock	12	8.1		12	12	9	Lack of

Actual Treatment	Unique Subject Identifier	Age/Sex/ Race	Dictionary-Derived Term	Study Day of Death	(Days) Exposure to Treatment	APACHE Score at Baseline	Start of AE Study Day of	End of AE Study Day of	to Treatment Day of Last Exposure	of Study Drug Discontinuation Reason
	001					11				Efficacy
	1008-6652-015	58/M/W	Road traffic accident	24	4.6	8	24	24	6	
	1008-7404-006	80/F/W	Septic shock	4	2.5	14	4	4	4	Adverse Event
	1008-8106-004	41/M/W	Cardiovascular insufficiency	2	0.4	10	2	2	2	Adverse Event
	1008-8108-001	88/F/W	Pulmonary embolism	14	8.4	16	11	14	10	
	1009-6477-006	69/M/W	Graft infection	30	4.6	9	16	30	6	
		69/M/W	Atrial fibrillation	30	4.6	9	16	30	6	
	1009-6477-008	81/F/W	Myocardial infarction	9	7.6	12	8	9	9	Adverse Event
Ceftolozane/Tazobactam+ Metronidazole	1008-4020-013	81/F/W	Lung infection pseudomonal	30	5.7	12	25	30	7	Lack of Efficacy
	1008-4127-002	66/M/W	Cardiac failure	9	8.7	14	9	9	9	Adverse Event
	1008-4127-025	73/M/W	Multi-organ failure	22	6.8	14	22	22	8	Lack of Efficacy
	1008-4714-008	81/M/W	Multi-organ failure	15	2.7	7	4	15	4	Adverse Event
			Ischemic stroke		2.7	7	3	15	4	Adverse Event
	1009-4206-003	55/F/W	Renal failure acute	32	5.9	6	23	32	7	Adverse Event
	1009-4811-003	74/F/W	Myocardial infarction	20	4.8	11	20	20	6	
	1009-5412-001	59/F/W	Sudden death	12	9.8	8	12	12	11	
	1009-6275-019	79/M/W	Sudden death	3	1.1	18	3	3	2	Adverse Event
	1009-6276-006	60/M/W	Septic shock	11	9	14	10	11	10	
			Multi-organ failure		9		10	11	10	

Actual Treatment	Unique Subject Identifier	Age/Sex/ Race	Dictionary-Derived Term	Study Day of Death	(Days) Exposure to Treatment	APACHE Score at Baseline	Start of AE Study Day of	End of AE Study Day of	to Treatment Day of Last Exposure	of Study Drug Discontinuation Reason
						14				
	1009-6376-009	76/F/W	Cardiogenic shock	7	5.1	10	7	7	6	Adverse Event
	1009-9003-001	80/F/W	Cardiopulmonary failure	3	1.4	6	2	3	3	Adverse Event
Phase 2 cIAI study										
	1001-9312-IA117	48/M/B	Renal Failure	8	1.4	missing	2	8	6	Adverse Event
	1001-7302-IA052	43/F/W	Pulmonary embolism	28	6	7	11	28	5	
	1001-7107-IA023	83/F/W	Urosepsis	8	6	10	8	9	3	
Phase 3 cUTI study										
	1005-5802-005	79/F/W	Bladder cancer	43	5.33	N/A	4	43	6	Adverse Event

The baseline APACHE scores split in three categories (below 10, from 11 to 14 and greater than 15) in the MITT population and the distribution of deaths by APACHE score categories and by treatment arm is shown in the table below.

Table 56: Phase 3 cIAI deaths distributions by APACHE scores

APACHE score categories	Ceftolozane/tazobactam plus metronidazole (number of deaths/N)	Meropenem (number of deaths/N)
<10	4/333 (1.2%)	3/363 (0.8%)
11 to 14	6 of 41 (14.6%)	4 of 33 (12.1%)
>15	1 of 13 (7.6%)	1 of 18 (5.5%)

The number of subjects with a baseline APACHE score >10 in the MITT population was slightly higher in the ceftolozane/tazobactam plus metronidazole arm (54 versus 51 in the meropenem

arm). Higher rates of deaths were observed in subjects with an APACHE score in the categories of 11-14 and >15 in both treatment arms. The distribution of deaths by APACHE score categories was similar in both treatment arm, with slightly higher rates in the ceftolozane/tazobactam plus metronidazole arm across all APACHE score categories, suggesting that this trend was observed independently of baseline disease severity. It is not possible to draw definitive conclusions from these small subgroups, since these distributions could have also occurred at random. However, it is also possible that the differences in death rates may reflect the overall difference in efficacy observed between study arms. In the ceftolozane/tazobactam plus metronidazole arm, all the deaths but one (subject 1009-4206-003, who died on study day 32) occurred within 30 days of study start, in both phase 2 and phase 3 studies. In the meropenem arm all deaths occurred within 30 days from study start. The deaths were a result of a combination of factors, mainly complications of the intra-abdominal infection and/or surgery and underlying co-morbidities, mostly cardiovascular and respiratory chronic conditions.

Baseline Demographic Characteristics of Subjects with Fatal Outcomes

The baseline characteristics of the subjects who died in the phase 3 cIAI study were reviewed in both treatment arms and relative to those of the whole MITT population. A few differences were noted, even though the small numbers in each category does not allow for formal statistical comparisons. In the table below, baseline characteristics of the MITT population are presented first in each row. The baseline characteristics of the 19 patients who died (11 in the ceftolozane/tazobactam arm and 8 in the meropenem arm are presented next to those of the MITT population, in the corresponding rows. The highlighted rows show main differences observed in some categories between study arms. These differences suggest that some baseline characteristics (older age, abnormal renal function, and need for a laparotomy procedure) may have adversely affected the outcomes observed in the treatment arm versus the comparator arm. However, in the MITT population, as the table below shows, the number of subjects with infections originating in the bowel, a known risk factor for worse prognosis, and subjects with polymicrobial infections, were higher in the meropenem arm. Besides, deaths rates were consistently higher in in the ceftolozane/tazobactam arm across all categories of APACHE scores (which take into account co-morbid conditions, severity of disease and other risk factors). Therefore, it is not possible to attribute the differences in death rates only to baseline characteristics differences. However, it is also possible that these differences could have occurred at random.

Table 57: Phase 3 cIAI study – Baseline characteristics (MITT population and subset of deaths)

	Ceftolozane/Tazobactam + Metronidazole N=389 (%)	n (%) **Deaths (N=11)**	Meropenem N=414 (%)	n (%) **Deaths (N=8)**
Age				
>=18 and <65	289 (59.9%)	2(0.6%)	330 (79.7%)	4(1.2%)
>=65 and <75	53 (13.6%)	3 (5.6%)	48 (11.5%)	1 (2.1%)
>= 75	46 (11.8%)	6 (13%)	36 (8.6%)	3 (8.3%)

Sex				
Female	169 (43.4%)	6 (3.5%)	169 (40.8%)	4 (2.4%)
Male	219 (56.2%)	5 (2.3%)	245 (59.1%)	4 (1.6%)
Race				
Asian	11 (2.8%)	0	14 (3.3%)	0
Black or African American	3 (0.7%)	0	2 (0.4%)	0
Not Applicable	1 (0.2%)	0	0	0
Other	7 (1.7%)	0	11 (2.6%)	0
White	366 (94%)	11 (3.0%)	387 (93.4%)	8 (2.1%)
Region				
Eastern Europe	297 (76.3%)	9 (3.0%)	307 (74.1%)	5 (1.6%)
North America	26 (6.8%)	1 (3.8%)	24 (5.7%)	0
Rest of the World	18 (4.6%)	0	19 (4.5%)	2 (10%)
South America	36 (9.2%)	1 (2.7%)	45 (10.8%)	1 (2.2%)
Western Europe	11 (2.8%)	0	19 (4.5%)	0
Site of Infection				
Bowel (small or large)	95 (24.4%)	8 (8.4%)	104 (25.1%)	5 (4.8%)
Other site of IAI	293 (75.3%)	3 (1.0%)	310 (74.8%)	3 (0.9%)
Baseline Creatinine				
>= 30 - < 50 mL/min (moderate impairment)	23 (5.9%)	4 (17%)	13 (3.1%)	1 (7.6%)
>= 50 - < 80 mL/min (mild impairment)	97 (24.9%)	6 (6.1%)	107 (16.9%)	4 (3.7%)
>= 80 mL/min (normal)	268 (68.8%)	1 (0.3%)	294 (71%)	3 (1.0%)
Procedure Type				
Laparoscopy	86 (22.1%)	1 (1.2%)	104 (25.1%)	2 (1.9%)
Laparotomy	273 (70.1%)	10 (3.6%)	268 (64.7%)	6 (2.2%)
Other	5 (1.2%)	0	4 (0.9%)	0
Percutaneous Aspiration	24 (6.1%)	0	37 (8.9%)	0
APACHE Score at Baseline				
< 10	310 (79.6%)	4 (1.3%)	343 (82.8%)	3 (0.8%)
>= 10	77 (19.7%)	7 (9.1%)	71 (17.1%)	5 (7.0%)
Abscess Type				
Multiple	33 (8.4%)	3 (9.0%)	31 (7.4%)	1 (3.2%)
Single	185 (47.5%)	2 (1.0%)	208 (50.2%)	3 (1.4%)
Number of Baseline Pathogens				
Monomicrobial	132 (33.9%)	2 (1.5%)	128 (30.9%)	2 (1.5%)
Polymicrobial	256 (65.8%)	9 (3.5%)	286 (69%)	5 (1.7%)
Abdominal Intervention relative to randomization				

Abdominal Intervention After Randomization	21 (5.3%)	1(4.7%)	26 (6.2%)	1 (3.8%)
Abdominal Intervention Prior to Randomization	367 (94.3%)	10(2.7%)	388 (93.7%)	7 (1.8%)

Deaths in the Phase 2 studies

Three subjects died during the cIAI study; all 3 were in the CXA-101/tazobactam group and all events leading to death were reported as unrelated to study treatment. The frequency of deaths in the phase 2 study was 3.7% (3/82) vs. 0% (0/39) in the meropenem arm. There were no deaths in the cUTI phase 2 trial. Brief narratives for each of these 3 subjects from the phase 2 cIAI study follow:

- Subject 7107-IA023 was an 83-year-old female with medical history significant for diabetes mellitus, chronic pancreatitis, encephalopathy, hepatitis C, ischemic heart disease with hypertension and angina, and chronic pancreatitis. The subject was entered onto the study following laparotomy for drainage of a retroperitoneal abscess with diffuse peritonitis caused by *K. pneumoniae*. She received 7 days of study treatment and was reported as clinically improved at the end of therapy. Three days after the EOT visit, the subject developed urosepsis with pulmonary edema requiring mechanical ventilation and rapidly deteriorated and died on the same day. Autopsy revealed chronic pyelonephritis with paranephric abscess and generalized peritonitis. The death was assessed as unrelated to study treatment.
- Subject 7302-IA052 was a 43-year-old female with medical history significant only for Hashimoto's disease. The subject was entered onto the study following laparotomy with Hartmann procedure for treatment of perforation due to diverticular disease; causative pathogens were *E. coli, E. cloacae*, and *B. fragilis*. She received 7 days of study treatment and was reported as a clinical failure at EOT requiring additional antibiotic therapy. She was switched to imipenem 1 day after the end of study drug therapy. She subsequently experienced ischemic colitis with fecal discharge from the surgical wound and underwent resection of the colon due to necrosis and perforation 6 days post-treatment and was placed on vancomycin plus fluconazole with the addition of ciprofloxacin 13 days post-treatment. Three weeks following study treatment the subject developed a pulmonary embolus (complication following deep vein thrombosis) with cardiac arrest and died. The death was assessed as unrelated to study treatment.
- Subject 9312-IA117 was a 48-year-old male with medical history significant for morbid obesity, myocardial infarction, hypertension, atrial fibrillation, ventricular pacemaker, diabetes mellitus, and chronic obstructive pulmonary disease, who experienced multi-organ failure related to septic shock prior to study entry. The subject was entered onto the study following small bowel resection for a strangulated ventral hernia. He was enrolled in violation of the protocol's inclusion/exclusion criteria, including open-abdomen technique, unlikely to survive the study period, and pre-existing multi-organ failure. Study drug was discontinued due to the protocol violations after only 2 doses. One day post-treatment discontinuation, the subject developed worsening renal failure,

pulmonary edema and atelectasis. He died 7 days post-treatment (cause of death: cardio-respiratory arrest) following multiple re-explorations of the original laparotomy. The death was assessed as unrelated to treatment with CXA-101/tazobactam.

Medical Reviewer comments: I reviewed the narratives and the case report forms of these patients and agree with the results presented by the applicant. Cardiovascular events and complications of the underlying infection were the most frequent causes of death in both arms. There was one death in the cUTI trial, due to bladder cancer and it was clearly not temporally or causally related to the study drug. In the cIAI trial, all deaths but one had an originating site of infection other than the appendix. The colon was the most common site involved in the ceftolozane/tazobactam arm (9 subjects); small bowel, cholecystitis and appendix were the sites in the other 3 subjects in this arm. In the meropenem arm, 2 subjects had colon as primary site and 3, small bowel; 4 others had cholecystitis. A higher mortality is expected from surgical infections arising from the large and small bowel sites. There was a higher number of deaths in the ceftolozane/tazobactam arm, 11 vs. 8 in the meropenem arm. There was a higher number of subjects with infections originating in the colon as a site in the ceftolozane/tazobactam arm, and more subjects in the ceftolozane/tazobactam arm had an APACHE score >10 at baseline than in the meropenem arm (8 vs. 5 subjects in the ceftolozane/tazobactam arm and in the meropenem arm, respectively). Patients who died in the ceftolozane/tazobactam arm were slightly older (mean age 72 and median of 75 years in the ceftolozane/tazobactam arm vs 67 and 66 years, respectively, in the meropenem arm). A combination of predisposing chronic heart and lung diseases and the underlying infection arising mainly from colon and bowel sites are the most likely reasons for these deaths in the cIAI study. The slight imbalance in deaths for the ceftolozane/tazobactam arm was driven by cardiac events (4 vs 3 events in the meropenem arm) and general disorders and administration conditions (where 3 multi-organ failures and 2 sudden deaths were classified in the ceftolozane/tazobactam arm, vs 0 in the meropenem arm). These were patients who presented several high risk conditions and co-morbidities. In at least two of the multi-organ failure cases and one of the sudden death cases a lack of efficacy of the study drug cannot be ruled out, however, as a contributing factor. This possibility of lack of efficacy is less likely in subjects 1008-4714-008 and 1009-6275-019, because of the short amount of exposure, the lack of clear temporal association and the presence of other significant co-morbidities at the time of death.

In the cUTI trial, only one death occurred and in a subject with bladder cancer. The imbalance in the number of deaths between the cUTI and cIAI trials is a reflection of the higher severity of the underlying illness of the patient population with cIAI. It is difficult to determine with certainty the possible contribution of toxicity of the study drug to these events, especially, in the presence of several alternative etiologies, and the complex combination of predisposing conditions and disease severity. However, a potential lack of efficacy cannot be ruled out and it is possible as a contributing factor to these deaths in the cIAI study. The mortality rate in the study is consistent with what is expected for these high risk patients. The overall difference in mortality rate of ceftolozane/tazobactam arm vs. meropenem in the phase 3 cIAI studies is 1%; however, this is not statistically significant.

The deaths in the phase 2 study were imbalanced in the ceftolozane/tazobactam arm (3.7% vs. 0%), however, the 2:1 randomization in this study and the small number of subjects are limitations to making conclusions. The causes of deaths in this study represent treatment failures in two of the three cases. The third subject had a violation of the protocol's inclusion/exclusion criteria, an open-abdomen technique surgery, unlikely to survive the study period, and pre-existing multi-organ failure. My conclusion is that the deaths observed in the ceftolozane/tazobactam arm are of similar nature and timing as those in the meropenem arm, with a slightly higher number of deaths occurring in the ceftolozane/tazobactam arm. All but one death occurred within 30 days of the study start, and deaths were due to a combination of underlying morbidities and complications of the intra-abdominal infection. A potential lack of efficacy from ceftolozane/tazobactam cannot be excluded as a contributing factor.

7.3.2 Nonfatal Serious Adverse Events

There were a total of 108 (5%) of 2047 subjects with serious adverse events in the integrated phase 3 studies, including the 20 subjects who died. Overall, the incidence of other SAEs was low and balanced across treatment arms in the clinical program. The majority of SAEs were assessed as unrelated to study drug. The SAEs reported were mostly related to the subjects' underlying disease or complications of the surgical treatment, and were primarily infection-related events. The table below, presented by the applicant, shows the serious adverse events occurring in the integrated phase 3 studies, in more than one subject per category.

Table 58: Serious Treatment-emergent Adverse Events by Preferred Term Occurring in More than One Subject in the Integrated Phase 3 cUTI and cIAI Studies (Safety Population)

Preferred Term	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
	Ceftolozane/ Tazobactam (N=533) n (%)	Levofloxacin (N=535) n (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n (%)	Meropenem (N=497) n (%)	Ceftolozane/ Tazobactam (N=1015) n (%)	All Comparators (N=1032) n (%)
Any Serious Treatment-emergent Adverse Event	15 (2.8)	18 (3.4)	39 (8.1)	36 (7.2)	54 (5.3)	54 (5.2)

Urinary tract infection	3 (0.6)	2 (0.4)	1 (0.2)	0	4 (0.4)	2 (0.2)
Abdominal abscess	1 (0.2)	0	2 (0.4)	2 (0.4)	3 (0.3)	2 (0.2)
Multi-organ failure	0	0	3 (0.6)	0	3 (0.3)	0
Septic shock	0	0	3 (0.6)	2 (0.4)	3 (0.3)	2 (0.2)
Bladder cancer	2 (0.4)	0	0	0	2 (0.2)	0
Clostridium difficile colitis	1 (0.2)	0	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.1)
Ischaemic stroke	0	0	2 (0.4)	0	2 (0.2)	0
Pneumonia	2 (0.4)	0	0	2 (0.4)	2 (0.2)	2 (0.2)
Sudden death	0	0	2 (0.4)	0	2 (0.2)	0
Urosepsis	2 (0.4)	0	0	0	2 (0.2)	0
Wound evisceration	0	0	2 (0.4)	0	2 (0.2)	0
Acute respiratory distress syndrome	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Anastomotic leak	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Cardiac failure	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Ileus	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Liver abscess	1 (0.2)	0	0	3 (0.6)	1 (0.1)	3 (0.3)
Myocardial infarction	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Nausea	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Pelvic abscess	0	0	1 (0.2)	2 (0.4)	1 (0.1)	2 (0.2)
Pseudomembranous colitis	1 (0.2)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Respiratory distress	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)

Respiratory failure	0	0	1 (0.2)	2 (0.4)	1 (0.1)	2 (0.2)
Small intestinal obstruction	0	0	1 (0.2)	2 (0.4)	1 (0.1)	2 (0.2)
Wound dehiscence	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Bile duct stone	0	0	0	2 (0.4)	0	2 (0.2)
Pyelonephritis	0	6 (1.1)	0	0	0	6 (0.6)
Sepsis	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)
Subdiaphragmatic abscess	0	0	0	2 (0.4)	0	2 (0.2)
Transient ischaemic attack	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; n = number of subjects in specific category; N = number of subjects in the Safety population. Source: M5.3.5.3 ISS\Section 2.1\Table 16

The incidence of SAEs was similar in the integrated ceftolozane/tazobactam treatment arm (54 subjects, 5.3%) and the comparator treatment arm (54 subjects, 5.2%). In both the cUTI and cIAI indications, the incidence of SAEs was comparable between treatment arms. As expected, there was a higher incidence of SAEs in the cIAI indication consistent with the severity of the disease and surgical intervention. Most SAEs were single events and were most commonly reported in the Infections and Infestations SOC (pneumonia, bacteremia, abscess, sepsis, and pyelonephritis).

In subjects with cUTI, SAEs were reported in 15 (2.8%) subjects in the ceftolozane/tazobactam treatment arm and 18 (3.4%) subjects in the levofloxacin treatment arm. All but 2 events (*C. difficile* colitis and pseudomembranous colitis) in the ceftolozane/tazobactam treatment arm were assessed by the primary investigator as unrelated to study drug.

Serious Adverse Events related to study drug

One SAE in the ceftolozane/tazobactam arm plus metronidazole in the cIAI indication was considered related to study drug. The event was *Clostridium difficile* colitis in a 69 year old female from Hungary. The subject had acute cholecystitis and after surgery she received 5 days of therapy with ceftolozane/tazobactam plus metronidazole. She presented diarrhea and abdominal pain and was admitted to the hospital 4 days after last dose of study therapy. The stool samples were positive for C. difficile antigen. The subject was treated with oral metronidazole and had a successful outcome, discharged to home 10 days after the last study drug dose.

One episode of *C. difficile* colitis was also reported in the meropenem arm, as an SAE also, in the cIAI study. Two additional cases (one *C. difficile* and one pseudomembranous colitis) were observed in the meropenem arm, not reported as SAE.

Three cases of *Clostridium difficile* infection (2 *C. difficile* and one pseudomembranous colitis) occurred in the ceftolozane/tazobactam arm compared to no cases in the levofloxacin arm. Two of these cases were SAEs and all 3 were considered drug-related. The study protocol did not require testing for *C. difficile* in the event of diarrhea. Overall, diarrhea was reported more frequently in the levofloxacin arm, and 19/23 (83%) cases in the levofloxacin arm were categorized as drug related by the investigator, compared to 4/10 (40%) cases in the ceftolozane/tazobactam arm. It is likely that *Clostridium difficile* infection cases were underreported and underdiagnosed in both arms.

In general, in subjects with cIAI, the incidence of SAEs was comparable between treatment arms (39 [8.1%] versus 36 [7.2%] in the ceftolozane/tazobactam plus metronidazole and meropenem arms respectively). Events in the Infections and Infestations were the more frequent ones in both arms (11 [2.3%] in the ceftolozane/tazobactam arm and 21 [4.2%] in the meropenem arm, and these included sepsis, abdominal abscesses, urinary infections, pneumonia and bacteremia. These events occurred at a similar time (median study day of 13 and 10 in the ceftolozane/tazobactam and meropenem arm, respectively) and represented complications of the infection, relapses or lack of efficacy. Gastrointestinal events were the second most common (10 [2.1%] and 3 [0.6%] in the ceftolozane/tazobactam arm and in the meropenem arm, respectively. These events included intestinal obstructions and/or perforations, intestinal ischemia, intestinal fistula, intestinal bleeding, nausea and vomiting. They occurred at a median study day of 12 and 13 in the ceftolozane/tazobactam arm and in the meropenem arm, respectively. They represented complications of the infection, the underlying conditions and/or the surgery.

In the cIAI indication, cardiac-related SAEs were comparable between treatment arms (4 [0.8%] subjects in both the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms). They were assessed by the investigator as unrelated to study drug, and resulted in death in 7 of the 8 subjects affected. The applicant states that the similar incidence in both treatment arms in the cIAI indication, and absence of serious cardiac events in the ceftolozane/tazobactam treatment arm of the cUTI indication, suggests that these events were related to the subjects' underlying condition, co-morbidities, and/or surgery rather than study drug. However, there were two sudden deaths and three multi-organ failure cases in the ceftolozane/tazobactam arm, which were not observed in the meropenem arm and were classified under general disorders and administration site conditions. A review of these cases suggests that a potential lack of efficacy in addition to severe underlying conditions cannot be excluded. These cases are discussed in section 7.3.1. There were also three cases of septic shock in the ceftolozane/tazobactam arm and two in the meropenem arm, mostly resulting from worsening of the underlying infection. The two tables below show the type of events that occurred more frequently in the ceftolozane/tazobactam arm and those occurring more frequently in the meropenem arm. In all cases, the differences in number of subjects were small; however, if grouped by type of events certain differences can be observed and will be discussed below. The two tables below present

the exploratory risk assessment of SAEs (SAEs with risk differences >1 in the ceftolozane/tazobactam and in the meropenem arm, respectively).

Table 59: Serious Adverse Events more frequent in Ceftolozane/tazobactam arm vs Meropenem (Risk Difference >1)

	Ceftolozane/tazobactam + Metronidazole		**Meropenem**	
Preferred Term	**#Subjects**	**Percent**	**#Subjects**	**Percent**
Multi-organ failure	3	0.6	0	0.0
Sudden death	2	0.4	0	0.0
Wound evisceration	2	0.4	0	0.0
Ischaemic stroke	2	0.4	0	0.0
Thrombocytosis	1	0.2	0	0.0
Cardiogenic shock	1	0.2	0	0.0
Cardiopulmonary failure	1	0.2	0	0.0
Enterocutaneous fistula	1	0.2	0	0.0
Upper gastrointestinal haemorrhage	1	0.2	0	0.0
Ileus paralytic	1	0.2	0	0.0
Rectal perforation	1	0.2	0	0.0
Duodenal ulcer haemorrhage	1	0.2	0	0.0
Intestinal perforation	1	0.2	0	0.0
Large intestine perforation	1	0.2	0	0.0
Small intestinal perforation	1	0.2	0	0.0
Intestinal ischaemia	1	0.2	0	0.0
Portal vein thrombosis	1	0.2	0	0.0
Lung infection pseudomonal	1	0.2	0	0.0
Pneumonia staphylococcal	1	0.2	0	0.0
Staphylococcal bacteraemia	1	0.2	0	0.0
Abdominal infection	1	0.2	0	0.0
Infectious peritonitis	1	0.2	0	0.0
Peridiverticular abscess	1	0.2	0	0.0
Urinary tract infection	1	0.2	0	0.0
Anaemia postoperative	1	0.2	0	0.0

Suture rupture	1	0.2	0	0.0
Hepatic enzyme increased	1	0.2	0	0.0
Decreased appetite	1	0.2	0	0.0
Colon cancer	1	0.2	0	0.0
Renal failure acute	1	0.2	0	0.0
Atrophic vulvovaginitis	1	0.2	0	0.0
Pleurisy	1	0.2	0	0.0
Pleural effusion	1	0.2	0	0.0
Shock haemorrhagic	1	0.2	0	0.0
Deep vein thrombosis	1	0.2	0	0.0
Pelvic venous thrombosis	1	0.2	0	0.0
Septic shock	3	0.6	2	0.4

Table 60: Serious Adverse Events more frequent in the Meropenem arm (Risk Difference >1)

	Meropenem		**Ceftolozane/tazobactam + Metronidazole**	
Preferred Term	**#Subjects**	**Percent**	**#Subjects**	**Percent**
Small intestinal obstruction	2	0.4	1	0.2
Pelvic abscess	2	0.4	1	0.2
Respiratory failure	2	0.4	1	0.2
Atrial fibrillation	1	0.2	0	0.0
Cardiovascular insufficiency	1	0.2	0	0.0
Goitre	1	0.2	0	0.0
Vomiting	1	0.2	0	0.0
Non-cardiac chest pain	1	0.2	0	0.0
Bile duct stone	2	0.4	0	0.0
Biliary fistula	1	0.2	0	0.0
Perforation bile duct	1	0.2	0	0.0
Pseudomembranous colitis	1	0.2	0	0.0
Appendiceal abscess	1	0.2	0	0.0
Subdiaphragmatic abscess	2	0.4	0	0.0
Gallbladder abscess	1	0.2	0	0.0
Liver abscess	3	0.6	0	0.0

Device related infection	1	0.2	0	0.0
Graft infection	1	0.2	0	0.0
Lobar pneumonia	1	0.2	0	0.0
Pneumonia	2	0.4	0	0.0
Sepsis	1	0.2	0	0.0
Pneumoconiosis	1	0.2	0	0.0
Road traffic accident	1	0.2	0	0.0
Abdominal wound dehiscence	1	0.2	0	0.0
Dehydration	1	0.2	0	0.0
Muscular weakness	1	0.2	0	0.0
Transient ischaemic attack	1	0.2	0	0.0
Encephalopathy	1	0.2	0	0.0
Pneumonia aspiration	1	0.2	0	0.0
Pulmonary embolism	1	0.2	0	0.0
Circulatory collapse	1	0.2	0	0.0
Intra-abdominal haemorrhage	1	0.2	0	0.0

A detailed exploratory review of thrombotic and embolic events was conducted, because the standardized MedDRA query for thrombotic and embolic events (which includes stroke, myocardial infarction, venous and arterial thrombosis or embolism) showed a total of 9 cases vs. 3 in the meropenem arm, with a risk ratio greater than 5 for the ceftolozane/tazobactam plus metronidazole arm. Most of these cases were reported as SAEs (7/9 in the ceftolozane/tazobactam arm and 3/3 in the meropenem arm). The table below presents key information about the total of 12 cases. From the 9 cases in the ceftolozane/tazobactam arm, two cases of myocardial infarctions did not have a clear temporal association (occurred at study day 19 and 20, respectively). From the 3 cases in the meropenem arm, one case of transient ischemic attack did not have a clear temporal association (occurred at study day 27). In 3 cases of the ceftolozane/tazobactam arm, an increase in platelet counts was observed, temporally associated with treatment. In addition, there was also one case of thrombocytosis reported as an SAE that did not have clinical manifestations. In this patient, platelet counts increased to more than twice the baseline value and decreased to baseline after treatment. The subject had had a diagnosis of thrombocytosis two years prior, of unclear etiology. One case of ischemic stroke was diagnosed on study day 1, with short drug exposure. Another case of potential stroke was suspected but not confirmed, occurred at study day 4 to 6. Deep vein thrombosis, bowel ischemia and renal and spleen infarctions were observed only in the ceftolozane/tazobactam plus metronidazole arm. These two subjects,(1008-4127-020 and 1008-4023-004) were younger than 65 years old and had more than one event (venous and arterial) temporally associated to treatment (please see table below). Although surgery and obesity could have been risk factors contributing to these

events, these presentations are unusual (relatively young patients with more than one type of event post-abdominal surgery). The table below provides details on the thromboembolic events.

Table 61: Phase 3 Embolic and Thrombotic Events – SMQ N=12

Subject ID/ country	Age/Sex /Race	Diagnosis	Event	Day of Onset/ End	Days of Exposure	Significant Labs	SAE or No SAE/ Outcome
Ceftolozane/tazobactam + Metronidazole N=9							
1008-4127-020/ Slovakia	31/M/W	Intraabd. abscess liver and spleen	Portal vein thrombosis/ bowel ischemia	D4-D6 D4-D6	13.1	N/A	SAE/Cure
1009-5023-003/ USA	38/F/W	Upper GI perf. Roux, peritonitis	Deep vein thrombosis?	D18-D28	5.1	PLT 280 to 411	SAE/Cure
1008-4023-004/ USA	58/M/W	Traumatic perf. intestine	Acute respiratory insufficiency, atrial fibrillation, infarcts to kidney, spleen and entero-cutaneous fistula	D3-D20 D4- D19 D8-D15	7.6	N/A	SAE/Cure
1008-4717-002/ Russia	68/F/W	Upper GI perf. Abscess/peritonitis	Thrombophlebitis of the arm	D2-D38	7.8	PLT 308, 589, 757 PT 17.4	No SAE/Cure
1008-4127-014/ Slovakia	76/M/W	Diverticular perf. abscess	Thrombosis of left ileal vein/left leg, renal impairment, upper GI bleed	D12-D30	13.1	N/A	SAE/Cure
1009-4811-003/ Serbia	74/F/W	Cholecystitis, perf. gangrenous	Myocardial infarction	D19-D21	4.8	N/A	SAE/Failure (death)
1009-6679-002/ Latvia	72/F/W	Peritonitis perf. viscus following other procedure	Cerebrovascular insufficiency confusion	D4-D6	7.6	N/A	No SAE/Cure
1008-4713-007/ Russia	77/F/W	Appendiceal perforation/abscess	Ischemic stroke	D1-D7	6.1	PLT 288-355	SAE/Cure
1008-4714-008/ Russia	81/M/W	Peritonitis, perf viscus after other procedure	Ischemic stroke/ Multi-organ failure	D3-D15 D4-D15	2.7	N/A	SAE/ Indeterminate (death)
Meropenem N=3							
1008-8108-001/ Russia	88/M/W	Diverticular abscess	Pulmonary embolism	D11-D15	8.4	N/A	SAE/ Failure
1009-6477-008/ Israel	81/F/W	Peritonitis perforated viscus after prior surgery	Myocardial infarction	D8-D9	7.6	N/A	SAE/Indeterminate (death)
1009-4611-009/ Hungary	65/M/W	Appendiceal perforation	Transient ischemic attack	D27-D32	3.7	N/A	SAE/Cure

Medical Reviewer's comments: The rates and types of SAE were balanced in the cUTI trial. In the cIAI trial, SAE rates were comparable, with a slightly higher rate of SAEs in the ceftolozane/tazobactam + metronidazole arm versus meropenem (8.1% vs 7.2%). Regarding the types of SAEs in the ceftolozane/tazobactam + metronidazole, a higher number of deep venous thromboses was observed (a total of 4 cases vs. 0 in the meropenem arm). A higher number of ischemic strokes (2 vs. 0) was also observed. All subjects had predisposing conditions (e.g., ischemic heart disease, hyperlipidemia, hypertension) that could have contributed to these events. A higher incidence of thrombocytosis was also observed in the ceftolozane/tazobactam plus metronidazole arm versus meropenem (1.9% vs 1.0). Thrombocytosis and venous thrombotic events can result as a complication of severe infections and/or inflammatory conditions. These patients were receiving prophylactic anticoagulant therapy, as were subjects in the meropenem arm. The timing of these events is consistent with what is described in post-operative settings, within two to three weeks after surgery. One case of intestinal ischemia, vs. 0 in the meropenem arm was observed. In the phase 2 cIAI trial there was one case of intestinal ischemia vs 0 in the meropenem arm as well. There were also 4 cases of intestinal perforations (small and large intestine) in the ceftolozane/tazobactam arm vs. 0 in the meropenem arm. Two cases of intestinal perforation vs. 0 in the meropenem arm were also observed in the phase 2 cIAI trial. Intestinal perforations can be caused by intestinal ischemia or necrosis from worsening of the underlying infection and inflammatory responses to it, and/or predisposing host factors. A lack of efficacy of ceftolozane/tazobactam + metronidazole treatment and/or lack of control of the source of infection may have contributed to these events. The venous thrombotic events as well as the intestinal perforations were serious, prolonged hospitalizations and required additional treatments to prevent life-threatening and fatal outcomes. Given the multiple confounding factors, the severity of the underlying disease, the unknown effectiveness of the anticoagulation treatment received, and the unknown time of evolution of the infection before treatments were started, it is not possible to accurately evaluate the contribution of ceftolozane/tazobactam to these events. However, a drug effect cannot be ruled out completely, particularly because of the slight imbalance between treatment arms observed, despite the protective effect of randomization. A potential drug effect inducing a hypercoagulability state in some patients could be suggested by one preclinical study in rats, which showed thrombocytosis and shortened aPTT in the tazobactam alone and in the ceftolozane/tazobactam arms. The addition of ceftolozane did not have synergistic or additive effect to that of tazobactam alone. These findings were not observed in the ceftolozane alone arm. Other animal studies did not reproduce these findings.. However, an indirect effect due to lack of efficacy of ceftolozane/tazobactam + metronidazole in subjects who are more severely ill and/or have other predisposing conditions could not be ruled out. In Study CXA-REN-11-01, 1 out of the 6 subjects in the end-stage renal disease cohort in hemodialysis had thrombosis of an arteriovenous fistula, for which he had to be hospitalized for declotting procedure and heparin treatment. In the now cancelled open label nosocomial pneumonia study, 1 of 3 patients who received ceftolozane/tazobactam had severe bowel ischemia and died. Other confounding factors (hypertension, diabetes, old age) were present. A review of coagulation tests (PT/PTT) in clinical studies did not show a significant difference in treatment arms. There was, however, a higher rate of thrombocytosis in the cIAI study only (1.9% vs 1.0% subjects). The rates of

thrombocytosis were lower and comparable between treatment arms in the cUTI trial (0.5% in each arm).

In the meropenem arm, abdominal infections or abscesses were observed more frequently than in the ceftolozane/tazobactam arm (a total of 10 cases in the meropenem arm vs 6 cases in the ceftolozane/tazobactam + metronidazole arm). The finding of these abscesses also prolonged hospitalization and required drainage to control the infection. Abscesses in the meropenem arm occurred later, at a median study day from 13 to 29, and in the ceftolozane/tazobactam arm, at a median study day from 10 to 13. Most of them resolved with treatment, in both arms. A lack of source control in the initial surgery and/or a lack of efficacy of antibacterial treatment are possible causes for the formation of these abscesses. The incidence of pneumonia, wound complications and cardiac and cardiovascular events was similar in each treatment arm.

7.3.3 Dropouts and/or Discontinuations

In the integrated Phase 3 studies, 20 of 1015 (2.0%) subjects in the ceftolozane/tazobactam group and 20 of 1032 (1.9%) subjects in the comparator group discontinued study drug due to TEAEs.

Renal impairment (including AE terms of renal impairment, renal failure, and renal failure acute) was the only TEAE that led to discontinuation of study drug for more than 1 subject treated with ceftolozane/tazobactam in the integrated Phase 3 analysis (2 subjects in cUTI and 3 subjects in cIAI). All 5 subjects who discontinued study therapy because of renal impairment had at least mild renal impairment at baseline. In addition, one other subject in the ceftolozane/tazobactam arm of the cUTI trial, 1005-4182-006, discontinued the trial because of nephritis. The six cases will be discussed below. The table below shows the adverse events leading to discontinuations in the pooled phase 3 studies.

Table 62: Treatment-emergent Adverse Events by Preferred Term Leading to Discontinuation of Study Drug in More than 1 Subject in the Integrated Phase 3 cUTI and cIAI Studies (Safety Population)

Preferred Term	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
	Ceftolozane/ Tazobactam (N=533) n (%)	Levofloxacin (N=535) n (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n (%)	Meropenem (N=497) n (%)	Ceftolozane/ Tazobactam (N=1015) n (%)	All Comparators (N=1032) n (%)
Any TEAE Leading to Study Drug Discontinuation	7 (1.3)	9 (1.7)	13 (2.7)	11 (2.2)	20 (2.0)	20 (1.9)

Renal impairment[a]	2 (0.4)	0	3 (0.6)	0	5 (0.5)	0
Diarrhoea	0	2 (0.4)	1 (0.2)	0	1 (0.1)	2 (0.2)
Clostridium difficile colitis	0	0	0	2 (0.4)	0	2 (0.2)
Drug hypersensitivity	0	2 (0.4)	0	0	0	2 (0.2)
Dermatitis allergic	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; n = number of subjects in specific category; N = number of subjects in the Safety population; TEAE = treatment-emergent adverse event.
a Includes preferred terms of renal impairment, renal failure, and renal failure acute. Source:M5.3.5.3 ISS\Section 2.1\Table 14 and Table 14.1

In the cUTI trial, 7 subjects in the ceftolozane/tazobactam arm discontinued the study drug due to an adverse event, 5 of whom recovered (two with renal impairment, one with infusion site thrombophlebitis, one with vomiting and one with pseudomembranous colitis); one died from bladder cancer and 1 other recovered with persisting renal impairment. In the levofloxacin arm, a total of 9 subjects discontinued study drug due to an adverse event, and 8 of them recovered, while one patient had persistent respiratory distress, unlikely related to the drug. In the levofloxacin arm, 3 subjects discontinued the drug due to allergic dermatitis and hypersensitivity reaction, 2 subjects had diarrhea, one subject had sepsis, one had renal tubular acidosis and one had infusion site erythema.

In the cIAI trial, a total of 13 subjects in the ceftolozane/tazobactam arm had adverse events causing discontinuation of study drug, 7 subjects recovered from them, 5 others died from them. Of the five subjects who died, three had cardiac failure, one died from sudden death and one from ischemic stroke. Among the 7 subjects who recovered in the ceftolozane/tazobactam arm, there were 3 subjects with renal impairment/failure, 2 subjects with diarrhea and abdominal pain, one subject with hemorrhagic shock and one with cardiac discomfort. In the meropenem arm, a total of 11 subjects had adverse events causing discontinuations of study drug. Of these, 3 of them died, from cardiovascular insufficiency, myocardial infarction and septic shock, respectively. Of the remaining 8 subjects with discontinuation of study drug in the meropenem arm, 1 of them had respiratory distress, 2 had *Clostridium difficile* diarrhea, 1 had allergic dermatitis and the others had complications from surgery and/or underlying comorbidities (anastomotic fistula, acute pulmonary edema, bronchopneumonia).

Overall, the causes and proportions of discontinuations due to adverse events were comparable between the two treatment arms, with a slightly higher mortality in the ceftolozane/tazobactam arm, due to cardiovascular events and complications of the underlying infection and surgery, unlikely related to the study drug. There was a higher number of discontinuations due to renal impairment in the ceftolozane/tazobactam arm.

In the pooled phase 3 trials, a total of 6 subjects in the ceftolozane/tazobactam arm had discontinuation of the study drug due to renal disorders. Five subjects had renal impairment (coded as renal failure, renal failure acute and renal impairment) and one subject had nephritis. Only 1 subject in the comparator arm had a discontinuation due to renal tubular acidosis.

A detailed review of the 6 subjects in the ceftolozane/tazobactam arm who discontinued because of renal impairment showed that 3 of these subjects (subjects 1008-4127-024, 1008-4128-021 and 1004-005-003, were older than 75 years of age, had elevated creatinine at baseline, elevated BUN and were receiving concomitant medications with potential nephrotoxicity as well (analgesics and diuretics). All of them presented elevations of creatinine after 2 days of study drug and recovered with discontinuation of the drug. Subject 1004-430-004, a 54 year old female, discontinued the drug due to acute renal failure on Study Day 2. This subject had nephrolithiasis and hypertension, with an elevated creatinine at baseline. She was also receiving furosemide and analgesics. Subject 1008-700-004 was an 82 year old male with hypertension, dyspnea and peripheral edema who had elevated creatinine at baseline and developed worsening of renal function after two days of study medication. Subject 1005-8142 was a 29 year old male with pyelonephritis who had a normal creatinine at baseline and developed increased creatinine and leukocytes with increased basophils on study day 2 of ceftolozane/tazobactam. He also received diclofenac. The adverse event was entered as “paranephritis (the inflammation of connective tissue and fat around the kidney) on the right”. A sonogram revealed inflammation of the surrounding tissue of the right kidney. He was considered a treatment failure. The investigator characterized this as nephritis, not related to study drug. The patient had complete resolution of the event after study drug discontinuation and diclofenac discontinuation. He was treated with imipenem cilastatin.

In the Phase 2 studies, a total of 4 subjects had TEAEs leading to discontinuation of study drug, including 2 subjects with cIAI treated with ceftolozane/tazobactam (intestinal perforation and seroma), 1 subject with cUTI treated with ceftolozane (decreased creatinine clearance) and 1 subject with cUTI treated with ceftazidime (vomiting and diarrhea). The subject with decreased creatinine clearance, subject 2002-03-033, was a 71 year old female with complicated lower UTI and a baseline creatinine clearance of 51mL/min. She experienced a decrease of creatinine clearance on study day 3, when the drug was discontinued. The creatinine clearance returned to baseline after drug discontinuation. There was no other concomitant medication in this patient.

Across the Phase 1 studies, 3 subjects had TEAEs leading to study drug discontinuation, including 2 subjects who received ceftolozane/tazobactam (vomiting and pyrexia) and 1 who received piperacillin/tazobactam (hypersensitivity).

Medical Reviewer’s comments: The causes and proportions of drug discontinuations was balanced among the treatment arms in all phase 3 studies, except for cases of renal failure/renal impairment, which amounted to 6 cases in the ceftolozane/tazobactam arm vs. 1 case of renal tubular acidosis in the pooled comparator arms. One case of renal impairment was also observed in the Phase 2 study, in the ceftolozane/tazobactam arm only, which amount to a total

of 7 cases of discontinuations due to renal impairment in the whole development program (7 out of 1449 ceftolozane or ceftolozane/tazobactam recipients, or 0.48%). A detailed review of the 6 subjects in the ceftolozane/tazobactam arm who discontinued because of renal impairment showed that 3 of these subjects, were older than 75 years of age, had elevated creatinine at baseline, elevated BUN and were receiving concomitant medications with potential nephrotoxicity as well (analgesics and diuretics). All of them presented elevations of creatinine after 2 days of study drug and recovered with discontinuation of the drug. The other 3 subjects who were younger than 75 years old had other co-morbidities (nephrolithiasis, hypertension) and were receiving concomitant medications known to produce nephrotoxicity. All subjects recovered with discontinuation of study drug and other medications. The single case of renal impairment causing withdrawal of study drug in the phase 2 program had baseline normal renal function and reverted after drug discontinuation. The potential nephrotoxicity of ceftolozane/tazobactam causing drug discontinuations cannot be ruled out and it is suggested by the reversion of the renal function after drug discontinuation; however, in the presence of predisposing factors and concomitant nephrotoxic medications, it is likely that nephrotoxicity is the consequence of multiple factors in these patients. The incidence of renal impairment causing withdrawals in the clinical development program is below 1%.

7.3.4 Significant Adverse Events

The following organ systems and syndromes relevant to the cephalosporin class of antibacterials were analyzed for medically important categories of TEAEs associated with ceftolozane/tazobactam as follows:

- TEAEs indicating potential renal impairment
- TEAEs indicating potential drug-induced anemia
- TEAEs indicating potential liver injury
- TEAEs indicating potential antibiotic-associated diarrhea
- TEAEs indicating potential allergic reaction

Renal Organ System/Potential Renal Impairment

The incidence of acute renal failure, including events with preferred terms of renal impairment, renal failure, acute renal failure, and oliguria, was also low and comparable between treatment arms in the integrated Phase 3 studies. Eleven (1.1%) and 8 (0.8%) subjects in the ceftolozane/tazobactam and comparator treatment arms reported an acute renal failure event. The acute renal failure events generally represented shifts in renal function based on creatinine clearance occurring in subjects with at least mild renal impairment at baseline. All but 1 event each in the ceftolozane/tazobactam plus metronidazole and levofloxacin treatment arms were assessed as unrelated to study drug. A total of 6 subjects in the integrated phase 3 studies and 1 subject in the phase 2 studies discontinued treatment because of renal impairment. All these but one subject had elevated creatinine at baseline and other confounding factors.

Potential Drug-Induced Anemia

The overall incidence of anemia was low in the integrated phase 3 studies. Anemia was reported in less than 2% of the subjects across the development program and it was slightly more frequent in the cIAI study (1.24%) than in the cUTI (<1%). Anemia postoperative was reported in 2.07% of subjects in the cIAI study and in 1.61% of subjects in the meropenem arm. Standardized MedDRA queries (broad and narrow) showed low rates (between 1 and 2%) and no significant differences in rates for Hematopoietic erythropenia or Hemorrhage terms between treatment and comparator arms.

TEAEs indicating potential liver injury

Transient elevations in serum transaminases were observed in similar low rates in both treatment and comparator arms, most frequently in the cIAI study, during therapy; however, these elevations returned to the subject's baseline by the LFU visit. The low incidence and pattern of liver enzyme elevations and resolution were consistent with known experience for β-lactam therapy and comparable to levofloxacin and meropenem in the Phase 3 studies. Standardized MedDRA queries for broad and narrow terms related to drug related hepatic disorders, liver related investigations, signs and symptoms and severe hepatic disorders events showed low rates and comparable, slightly higher rates in the meropenem arm (3.7% and 5% in the ceftolozane/tazobactam and in meropenem arm respectively). However, there were a few more outliers with higher laboratory values of ALT or AST (>5 times ULN) and bilirubin (>2 times ULN) in the ceftolozane/tazobactam arm as compared with the meropenem arm, all peaking in the EOT visit and improving during the course of the study. No severe adverse events were reported in relation to these laboratory values. No additional tests were conducted to rule out alternative etiologies, other than the clinical evaluation of the underlying disease. In most cases these patients had gallbladder disease and infections extending beyond the gallbladder into the liver. This is described with more detailed below.

cIAI Potential Liver Injuries

Hy's Law laboratory cases

The applicant analyzed the data to determine if subjects met laboratory criteria for Hy's Law. Hy's Law criteria were met if they had the following from laboratory test results collected during a single visit:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3×ULN, and
- Total bilirubin ≥2×ULN, and
- Alkaline phosphatase ≤2×ULN

The applicant reported one subject in the ceftolozane/tazobactam plus metronidazole treatment arm met the criteria for Hy's law on study Day 3 but also met the criteria at screening. Since the time of onset was prior to the initiation of study drug therapy, the liver function test values declined while on therapy, no AEs indicative of hepatotoxicity were documented, and no similar

events were reported in the cUTI indication, the data do not suggest drug-induced liver disease with ceftolozane/tazobactam, although its contribution cannot be ruled out.

My review of the SDTM data with Empirica Study (Oracle, Inc.) found a total of 5 patients in the ceftolozane/tazobactam arm and 4 in the meropenem arm met the criteria for Hy's Law at post-baseline measurements; however, all but one of these patients (subject 1008-6650-021, summarized below) had elevated values at baseline also. In all cases, the most likely etiology was the underlying infection, which was severe cholecystitis with extension of the disease beyond the gallbladder wall in four cases and in one, peritoneal abscess with diffuse peritonitis and bowel perforation. All values improved during treatment which included surgery and study drug treatment.

In both the ceftolozane/tazobactam and in the meropenem arms, these cases presented early in the course of treatment (Days 1-4) and all improved during the course of treatment. In all 5 cases of the ceftolozane/tazobactam arm, the elevations in liver function tests meeting the Hy's Law criteria presented at the time of surgery (laparotomy in 4 cases and laparoscopic in 1). All patients had at least 6 days of treatment. One patient had an elevation of ALT >5 times the upper level of normal later in the study after treatment completion (Day 10). One other patient had acute pancreatitis. All patients recovered. A summary of the cases is presented below.

Subject 1009-4220-004: this subject was a 33 year old male who presented with appendiceal perforation with diffuse peritonitis. He also had diarrhea and pleuritic pain as adverse events. He received a single dose of ciprofloxacin and metronidazole prior to surgery. Other concomitant medications before and during the surgery were analgesic agents (diclofenac), muscle relaxants and anesthetic agents (suxamethomine chloride, propofol). The final assessment for this subject was clinical cure.

Subject 1008-4129-005: this subject was a 56 year old female who presented with a peritoneal abscess and diffuse peritonitis arising from bowel perforation. No adverse events were reported during the course of treatment. Concomitant medications included metamizole, omeprazole, muscle relaxants and anesthetic agents. She received one dose of ceftizoxime and metronidazole prior to surgery. The final assessment for this subject was clinical cure.

Subject 1008-4129-003: this subject was a 60 year old male who had a gastric and duodenal perforation with diffuse peritonitis for which he underwent a laparotomy. He received one dose of cefotaxime prior to surgery. Other medications included metamizole, pantoprazole, omeprazole and hyoscine. Analgesic agents and muscle relaxants were given during surgery (listed as phytomenadione and nadroparin calcium). The final assessment for this subject was clinical cure.

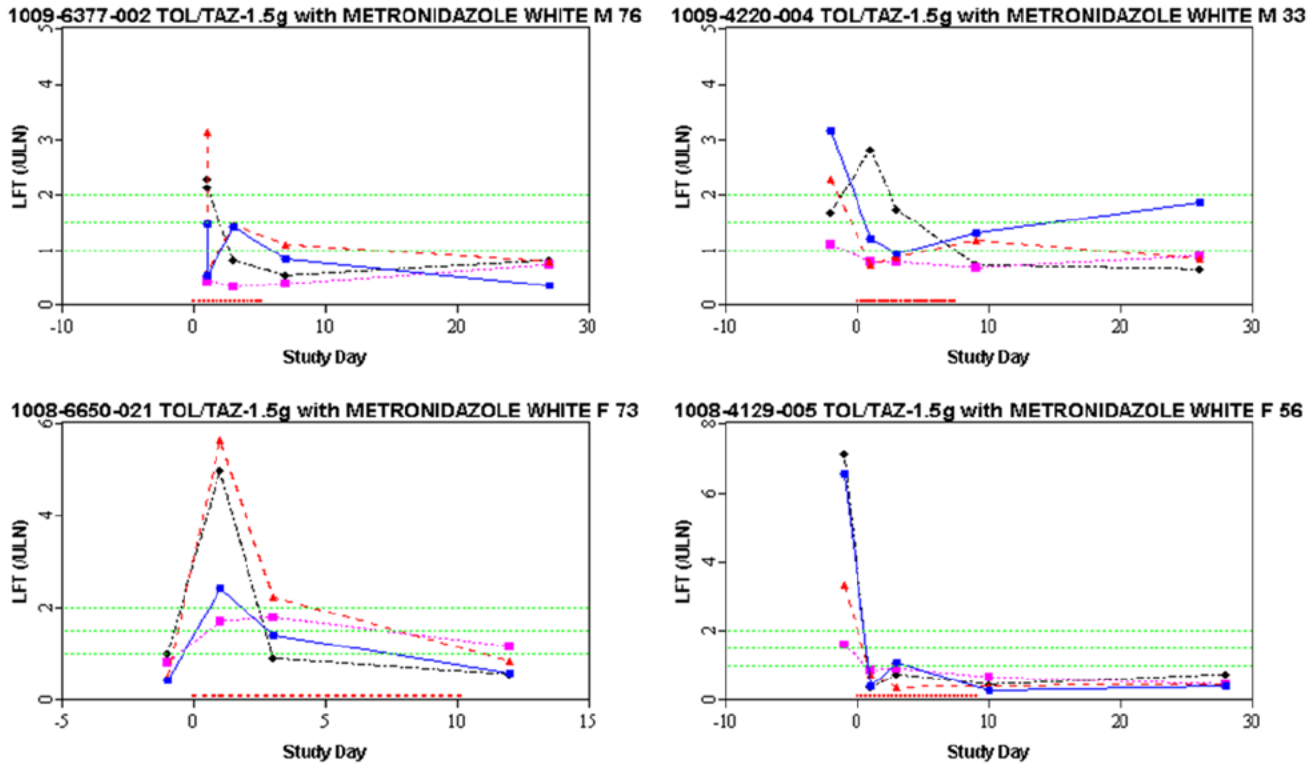
Subject 1008-6650-021: this subject was a 73 year old female who presented with gangrenous cholecystitis with perforation and extension of the abscess beyond the gallbladder. She also presented acute pancreatitis, not severe. Her concomitant medications included analgesic agents (diclofenac and morphine), anesthetic agents and muscle relaxants. The final assessment for this

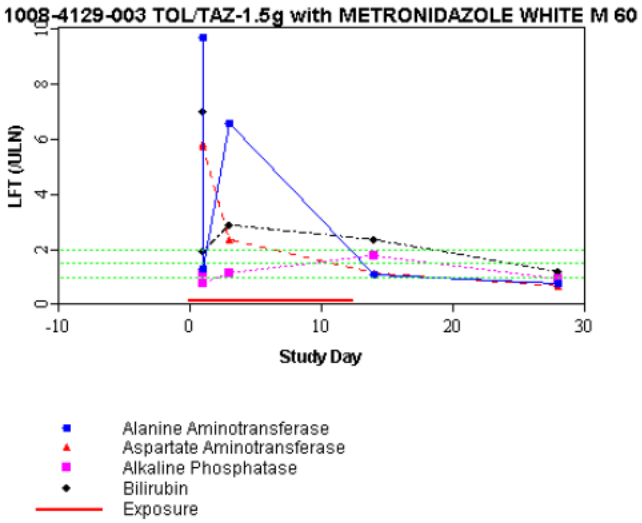
subject was clinical failure and the reason was the need to change antibacterial treatment to control the infection. The patient recovered after changing antibacterial therapy.

Subject 1009-6377-002: this subject was a 76 year old male who had gangrenous cholecystitis with abscess formation and extension beyond the gallbladder. He received single doses of ampicillin and gentamicin prior to surgery. Other concomitant medications were metamizole, anesthetic and muscle relaxant agents (propofol, drotaverine, suxamethonium). The final assessment for this subject was clinical cure.

The liver tests values for these 5 subjects are represented in the graphic below.

Figure 3: Liver Function Test Patient Profiles





Transaminases elevations at any time during the study

The proportions of transaminases elevations post-baseline occurring at the same visit at any time during the course of the study, not excluding subjects with abnormal baselines, are similar between treatment arms, and presented in the table below.

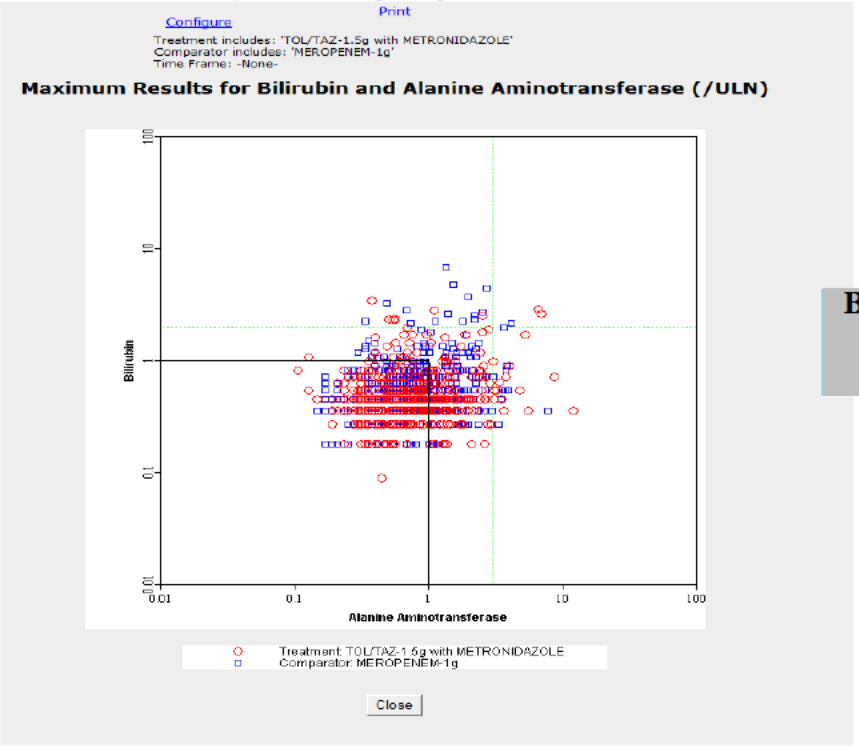
Table 63: cIAI study – Safety Population -Reviewer's table (SDTM data with Empirica Study)

	Treatment (N=482)		Comparator (N=497)		Total (N=979)	
Finding	**N**	**%**	**N**	**N**	**N**	**%**
(ALT or AST) >= 3x ULN, BILI >= 2x ULN, ALP <= 2x ULN	5	1%	4	0.8%	9	0.9%
(ALT or AST) >= 3x ULN, BILI >= 1.5x ULN, ALP <= 2x ULN	8	1.7%	5	1%	13	1.3%
(ALT or AST) >= 3x ULN, BILI >= 1.5x ULN	10	2.1%	7	1.4%	17	1.7%
(ALT or AST) >= 20x ULN	0	0%	0	0%	0	0%
(ALT or AST) >= 10x ULN	1	0.2%	1	0.2%	2	0.2%
(ALT or AST) >= 5x ULN	13	2.7%	8	1.6%	21	2.1%
(ALT or AST) >= 3x ULN	37	7.7%	37	7.4%	74	7.6%

In the Drug Induced Liver Injury (DILI) plot below, 4 subjects in each treatment arm presented elevations above 3 times ULN for ALT or above 2 times ULN for bilirubin. There is a

horizontal reference dotted line at 2x ULN for BILI. There is a **vertical** reference dotted line at 3x ULN for ALT. Solid lines represent ULN for both.

Figure 4: Maximum ALT and Bilirubin Values (above 3 times ULN for ALT and above 2 times ULN for Bilirubin), excluding subjects with abnormal baseline values.



Reviewer's comments: I agree with the applicant's conclusions; these liver tests abnormalities were observed early in the course of treatment and improved after the surgical procedure and during the course of treatment. The proportion of cases was low and similar to the comparator arm and all reverted during treatment. These patients had severe underlying infections and concomitant medications. The contribution of the study drug to these abnormalities cannot be ruled out; however, these were improved during treatment and they were not observed in the cUTI study. Therefore, it is more likely that these cases represent the effect of severe underlying infections, particularly involving the gallbladder and liver, plus the additional effect of concomitant medications and patient co-morbidities. One subject in each arm had elevations greater than 10 times the ULN of AST or ALT. Overall, a slightly higher number of subjects in the ceftolozane/tazobactam arm presented increases in ALT or AST above 5 times the ULN during the study than in the meropenem arm (2.7% vs 1.6% respectively). Elevations of AST or ALT above 3 times the ULN were similar in both arms (7.7% vs 7.4%). All elevations improved with treatment. No AEs indicative of hepatotoxicity were documented, and no similar events were reported in the cUTI indication; therefore, these data do not suggest drug-induced liver disease with ceftolozane/tazobactam as the cause for these observations, although the drug effect contribution to liver toxicity cannot be absolutely ruled out.

TEAEs Indicating Potential Antibiotic-Associated Diarrhea
In the integrated Phase 3 studies, a low and similar incidence of pseudomembranous colitis was reported in the ceftolozane/tazobactam and comparator treatment arms (0.4% and 0.3%, respectively). Adverse events terms within this category included *C. difficile* colitis, pseudomembranous colitis, and clostridial infection.

Pseudomembranous colitis events were reported in 3 (0.6%) subjects in the ceftolozane/tazobactam treatment arm in the cUTI indication and 1 (0.2%) subject in the ceftolozane/tazobactam plus metronidazole treatment arm and 3 (0.6%) subjects in the meropenem treatment arm in the cIAI indication. With the exception of 1 severe event of C. difficile colitis in the meropenem treatment arm, all events were moderate in severity, and all events recovered fully upon treatment.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The list of Adverse Drug Reactions (ADRs) was determined through clinical review of the TEAEs for possible causal relationship between ceftolozane/tazobactam and the event. The applicant's review included the following:

- TEAEs >1% in the integrated ceftolozane/tazobactam treatment arm;

- Investigator-assessed treatment-related TEAEs that occurred in at least 2 subjects;

- TEAEs where the incidence was higher in the integrated or by indication ceftolozane/tazobactam treatment arms versus the respective comparator treatment arm;

- Events that are known class effects of cephalosporins that were also observed in the Phase 3 cUTI and cIAI studies in the ceftolozane/tazobactam treatment arm; and

- Events that could plausibly be related to ceftolozane/tazobactam in light of its known pharmacology.

In addition, any rare typical drug-induced adverse reactions that did not fit the criteria above were reviewed. Based on these criteria, the applicant presented the following table:

Table 64: Adverse Drug Reactions by Preferred Term Occurring in ≥1% of Subjects in the Integrated Phase 3 cUTI and cIAI Studies (Safety Population)

Preferred Term	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
	Ceftolozane/ Tazobactam (N=533) n (%)	Levofloxacin (N=535) n (%)	Ceftolozane/ Tazobactam + Metronidazole (N=482) n (%)	Meropenem (N=497) n (%)	Ceftolozane/ Tazobactam (N=1015) n (%)	All Comparators (N=1032) n (%)
Nausea	15 (2.8)	9 (1.7)	38 (7.9)	29 (5.8)	53 (5.2)	38 (3.7)
Headache	31 (5.8)	26 (4.9)	12 (2.5)	9 (1.8)	43 (4.2)	35 (3.4)
Diarrhea	10 (1.9)	23 (4.3)	30 (6.2)	25 (5.0)	40 (3.9)	48 (4.7)
Constipation	21 (3.9)	17 (3.2)	9 (1.9)	6 (1.2)	30 (3.0)	23 (2.2)
Vomiting	6 (1.1)	6 (1.1)	16 (3.3)	20 (4.0)	22 (2.2)	26 (2.5)
ALT increased	9 (1.7)	5 (0.9)	7 (1.5)	5 (1.0)	16 (1.6)	10 (1.0)
AST increased	9 (1.7)	5 (0.9)	5 (1.0)	3 (0.6)	14 (1.4)	8 (0.8)
Abdominal pain	4 (0.8)	2 (0.4)	6 (1.2)	2 (0.4)	10 (1.0)	4 (0.4)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; n = number of subjects in specific category; N = number of subjects in the Safety population. Source: M5.3.5.3 ISS\Section 2.1\Table 7.2

Gastrointestinal events were the most frequently reported types of TEAEs in both studies. The 5 TEAEs with the highest incidence were nausea, headache, diarrhea, pyrexia, and constipation.

cUTI indication

The most frequently reported events in the ceftolozane/tazobactam treatment arm were headache (5.8%), constipation (3.9%), hypertension (3.0%), nausea (2.9%), and diarrhea (1.9%). Similarly, the TEAEs with the highest incidence in the levofloxacin treatment arm were headache (4.9%), diarrhea (4.3%), constipation (3.2%), nausea (1.7%), and urinary tract infection (1.7%).

cIAI indication

The TEAEs with the highest incidence in the ceftolozane/tazobactam plus metronidazole treatment arm were nausea (7.9%), diarrhea (6.2%), pyrexia (5.2%), insomnia (3.5%), and vomiting (3.3%). Similarly, the TEAEs with the highest incidence in the meropenem treatment arm were nausea (5.8%), diarrhea (5.0%), pyrexia (4.0%), vomiting (4.0%), and insomnia (2.2%).

7.4.2 Laboratory Findings

In the integrated Phase 3 studies, more than 95% of subjects had pre- and post-baseline laboratory data and the rates of missing tests at any time during the study was very low (less than 2% overall) and comparable between the treatment and comparator arms. The baseline laboratory values were similar between treatment and comparator arms in the integrated phase 3 studies.

Hematology
In the integrated Phase 3 analysis, shifts in hematology findings of 2 or more grades from baseline to any post-baseline assessment were observed for 11% of subjects in the ceftolozane/tazobactam treatment arm and 8% of subjects in the comparator treatment arm. The incidence of hematology shifts of 2 or more grades was higher in the cIAI indication (15% and 12% in the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively) compared with the cUTI indication (7% and 5% in the ceftolozane/tazobactam and levofloxacin treatment arms, respectively), likely due in part to the baseline surgery in the cIAI indication.
Overall, shifts from Grade 0, 1, or 2 at baseline to a worst value post-baseline of Grade 3 or 4 were uncommon for hematology parameters (<1% in each treatment arm for low hemoglobin, low neutrophils, and low platelets); however, shifts in leukocytes from normal or Grade 1 or 2 elevations at baseline to Grade 3 or 4 elevations post-baseline were observed in 6% of subjects in both treatment arms in the cIAI indication. The increases in leukocytes in these subjects largely occurred either early in therapy (Day 3) and resolved during therapy or occurred at the EOT in subjects with lack of response to therapy. The majority of subjects with worsening grade shifts had improved with respect to hematology parameters by the LFU visit.

Table 65: Shifts of 2 or More Grades From Baseline in Hematology Laboratory Findings at Any Time Post-Baseline in the Phase 3 cUTI and cIAI Studies (Safety Population)

Hematology Parameter	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
	Ceftolozane/ Tazobactam (N=533) n/N1 (%)	Levofloxacin (N=535) n/N1 (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n/N1 (%)	Meropenem (N=497) n/N1 (%)	Ceftolozane/ Tazobactam (N=1015) n/N1 (%)	All Comparators (N=1032) n/N1 (%)
Subjects with at Least 1 ≥2 Grade Shift from Baseline	30/451 (6.7)	22/455 (4.8)	60/400 (15.0)	50/411 (12.2)	90/851 (10.6)	72/866 (8.3)
Hemoglobin (low)	6/451 (1.3)	10/455 (2.2)	23/400 (5.8)	20/411 (4.9)	29/851 (3.4)	30/866 (3.5)

Leukocytes (high)	15/451 (3.3)	11/455 (2.4)	40/400 (10.0)	31/411 (7.5)	55/851 (6.5)	42/866 (4.8)
Neutrophils (low)	9/451 (2.0)	0	1/400 (0.3)	2/411 (0.5)	10/851 (1.2)	2/866 (0.2)
Platelets (low)	1/451 (0.2)	1/455 (0.2)	2/400 (0.5)	0	3/851 (0.4)	1/866 (0.1)

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; n = number of subjects with a shift of greater than or equal to two grades at any time
post-baseline relative to baseline, within a given laboratory parameter; N = number of subjects in the Safety population; N1 = number of subjects with a value at baseline and post-baseline. Source: M5.3.5.3 ISS\Section 2.1\Table 31.2

Coombs test

Direct Coombs tests were assessed as positive or negative and shifts from baseline (negative to positive or positive to negative) at the EOT visit were analyzed. In the integrated Phase 3 studies, 2 subjects in the ceftolozane/tazobactam treatment arm (1 subject in each indication) seroconverted from a negative to positive Coombs test at the EOT visit. One subject in the meropenem arm converted from negative to positive at EOT. No other laboratory abnormalities or study findings were indicative of hemolytic anemia in either of these subjects.

Clinical Chemistry Values

The baseline chemistry parameters were similar between the treatment arms in each Phase 3 study, and no major differences were seen in the magnitude of mean changes from baseline between the treatment arms over time for any chemistry parameter. In the integrated Phase 3 analysis, shifts in chemistry findings of 2 or more grades from baseline to any post-baseline assessment were observed in comparable proportions in the 2 treatment arms (26% of subjects in the ceftolozane/tazobactam treatment arm and 27% of subjects in the comparator treatment arm).

Table 66: Shifts of 2 or More Grades from Baseline in Chemistry Laboratory Findings at Any Time Post-Baseline in >1% of Subjects in the Integrated Ceftolozane/tazobactam or Comparator Treatment Arm in the Phase 3 cUTI and cIAI Studies (Safety Population)

Chemistry Parameter	Phase 3 cUTI		Phase 3 cIAI		Integrated Phase 3 cUTI and cIAI	
	Ceftolozane/ Tazobactam (N=533) n/N1 (%)	Levofloxacin (N=535) n/N1 (%)	Ceftolozane/ Tazobactam+ Metronidazole (N=482) n/N1 (%)	Meropenem (N=497) n/N1 (%)	Ceftolozane/ Tazobactam (N=1015) n/N1 (%)	All Comparators (N=1032) n/N1 (%)
Subjects with at Least 1 ≥2 Grade Shift from Baseline	83/514 (16.1)	75/517 (14.5)	169/448 (37.7)	191/466 (41.0)	252/962 (26.2)	266/983 (27.1)
Gamma Glutamyl Transferase	0	0	59/448 (13.2)	72/466 (15.5)	59/962 (6.1)	72/983 (7.3)
Hypophosphatemia (Phosphate)	0	0	55/448 (12.3)	67/466 (14.4)	55/962 (5.7)	67/983 (6.8)
Aspartate Aminotransferase	20/514 (3.9)	15/517 (2.9)	32/448 (7.1)	22/466 (4.7)	52/962 (5.4)	37/983 (3.8)
Alanine Aminotransferase	20/514 (3.9)	18/517 (3.5)	25/448 (5.6)	24/466 (5.2)	45/962 (4.7)	42/983 (4.3)
Hyperglycemia (Glucose)	21/514 (4.1)	19/517 (3.7)	17/448 (3.8)	19/466 (4.1)	38/962 (4.0)	38/983 (3.9)
Hypoglycemia (Glucose)	16/514 (3.1)	13/517 (2.5)	7/448 (1.6)	11/466 (2.4)	23/962 (2.4)	24/983 (2.4)
Hypocalcemia (Calcium)	0	0	21/448 (4.7)	14/466 (3.0)	21/962 (2.2)	14/983 (1.4)
Hyperkalemia (Potassium)	9/514 (1.8)	7/517 (1.4)	9/448 (2.0)	4/466 (0.9)	18/962 (1.9)	11/983 (1.1)
Hypokalemia (Potassium)	3/514 (0.6)	5/517 (1.0)	13/448 (2.9)	10/466 (2.1)	16/962 (1.7)	15/983 (1.5)
Alkaline Phosphatase	3/514 (0.6)	6/517 (1.2)	10/448 (2.2)	8/466 (1.7)	13/962 (1.4)	14/983 (1.4)
Hyponatremia (Sodium)	4/514 (0.8)	1/517 (0.2)	7/448 (1.6)	1/466 (0.2)	11/962 (1.1)	2/983 (0.2)
Hyperbilirubinemia (Bilirubin)	3/514 (0.6)	5/517 (1.0)	7/448 (1.6)	14/466 (3.0)	10/962 (1.0)	19/983 (1.9)

cIAI = complicated intra-abdominal infection; cUTI = complicated urinary tract infection; n = number of subjects with a shift of ≥2 grades at any time post-baseline relative to baseline, within a given laboratory parameter; N = number of subjects in the Safety population; N1 = number of subjects with a value at baseline and post-baseline. Source: M5.3.5.3 ISS\Section 2.1\Table 31.4

One subject with baseline severe renal impairment had worsening of Cr in the ceftolozane/tazobactam arm. This subject represented a protocol violation and the drug was discontinued. The Cr toxicity grade shifts in both treatment arms were otherwise mainly improvement in Cr, and no other subject discontinued the drug due to renal impairment. These chemistry laboratory shifts were more prevalent in the cIAI indication (38% and 41% in the ceftolozane/tazobactam plus metronidazole and meropenem treatment arms, respectively) compared with the cUTI indication (16% and 15% in the ceftolozane/tazobactam and levofloxacin treatment arms, respectively), reflecting the greater morbidity of the cIAI study population. Shifts from Grade 0, 1, or 2 at baseline to a worst value post-baseline of Grade 3 or 4 were generally uncommon for chemistry parameters. In the cUTI indication, shifts to Grade 3 or 4 occurred in no more than 2% of subjects for any parameter measured.

Laboratory Evaluations – cUTI study

Toxicity grades were as outlined in the Division of Microbiology and Infectious Diseases Adult Toxicity Table (November 2007).

There were no significant changes the mean and median hemoglobin and hematocrit and no differences in the two treatment arms at EOT or TOC visit. There were no differences in changes in leukocyte or platelet counts in the two treatment arms. One subject in the ceftolozane/tazobactam arm developed a positive Coombs test at the EOT visit without associated evidence of hemolysis or anemia.
Transient elevations of serum transaminases and/or bilirubin during treatment were observed in less than 1% of patients receiving ceftolozane/tazobactam, and were comparable to those in the comparator arm. The table below shows the elevations of different combination of liver parameters. No patient met Hy's law criteria.

Table 67: Subjects with Elevations of Liver Parameters – Phase 3 Study - cUTI

	Ceftolozane/Tazobactam N = 533	**Levofloxacin N = 535**
ALT		
Baseline		
ALT ≥3-<5x ULN	0/521	2/522 (0.4%)
ALT ≥5-10 x ULN	1/521 (0.2%)	0
EOT		
ALT ≥3-<5x ULN	5/513 (1.0%)	8/508 (1.6%)
ALT ≥5-10 x ULN	0	0
TOC		
ALT ≥3-<5x ULN	1/501 (0.2%)	3/501 (0.6%)
ALT ≥5-10 x ULN	0	0
Alkaline phosphatase >2xULN		
Baseline	1/513 (0.2%)	2/519 (0.4%)
EOT	4/508 (0.8%)	5/503 (1.0%)

TOC	2/501 (0.4%)	2/501 (0.4%)
Bilirubin >1.5xULN		
Baseline	9/515 (1.7%)	10/515 (1.9%)
EOT	0	0

There were no cases of Hy's law in either arm. No patient discontinued therapy due to a hepatic event.

In the cIAI indication, shifts to Grade 3 or 4 were most commonly observed for GGT (9% and 13% in the ceftolozane/tazobactam plus metronidazole treatment arm and meropenem treatment arms, respectively), low phosphate (4% and 7%, respectively), and AST (3% and 2%, respectively); no more than 2% of subjects had a shift to Grade 3 or 4 for any other chemistry parameter measured in either treatment arm. Of note, the shifts to Grade 3 or 4 elevations in liver function tests were rarely observed in the cUTI indication and did not occur in a higher incidence in the ceftolozane/tazobactam treatment arm versus the comparator treatment arm, suggesting that these elevations were probably not due to ceftolozane/tazobactam therapy. The liver function tests are discussed further in section 7.4.5.

7.4.3 Vital Signs

Descriptive statistics for the vital sign results at baseline, EOT, TOC, and highest and lowest post-baseline values for the integrated Phase 3 studies presented by treatment arm were reviewed.

Overall, there were no clinically meaningful changes in vital signs associated with ceftolozane/tazobactam in the integrated Phase 3 studies. The mean changes in heart rate, respiratory rate, temperature, and systolic and diastolic blood pressure from baseline were small and similar between the ceftolozane/tazobactam and comparator treatment arms. The mean decrease observed in heart rate and temperature during therapy in both treatment arms was consistent with subjects improving during the treatment of infection. There were no clinically meaningful differences between the ceftolozane/tazobactam and comparator treatment arms for clinically significant physical examination findings at the EOT or TOC visits.

7.4.4 Electrocardiograms (ECGs)

A Phase 1 healthy volunteer TQT study was conducted, and ECG results from this study are described below. Phase 3 studies did not include ECG assessments and Phase 2 studies included ECG assessments only at screening/baseline. The applicant's concluded that the TQT study was negative, with no findings indicating an effect of ceftolozane/tazobactam on cardiac repolarization. A consultation with the QT IRT group at CDER has been sent requesting a review of the results of the TQT study (CXA QT 10—2) and at the present time the results are pending. For more information, refer to the Clinical Pharmacology review done by Ryan Owen, PhD.

Study CXA QT-10-02 was performed to evaluate the effect of a single IV supra-therapeutic dose of ceftolozane/tazobactam on ventricular repolarization as measured by QTc to evaluate the change from the period-specific predose baseline of QT/QTc interval corrected by QTcI (individual correction subject-specific formula) across all dose groups. The results of this study demonstrate the absence of clinically relevant effects of a therapeutic and 3-fold supra-therapeutic dose of ceftolozane/tazobactam on ECG parameters, including the QTc interval.

None of the subjects had a QTc interval >480 ms and the number of subjects with individual QTc intervals >450 ms and increases in QTc from baseline >30 ms 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.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

Not applicable

7.5.1 Dose Dependency for Adverse Events

No particular dose dependency trends were observed for adverse events.

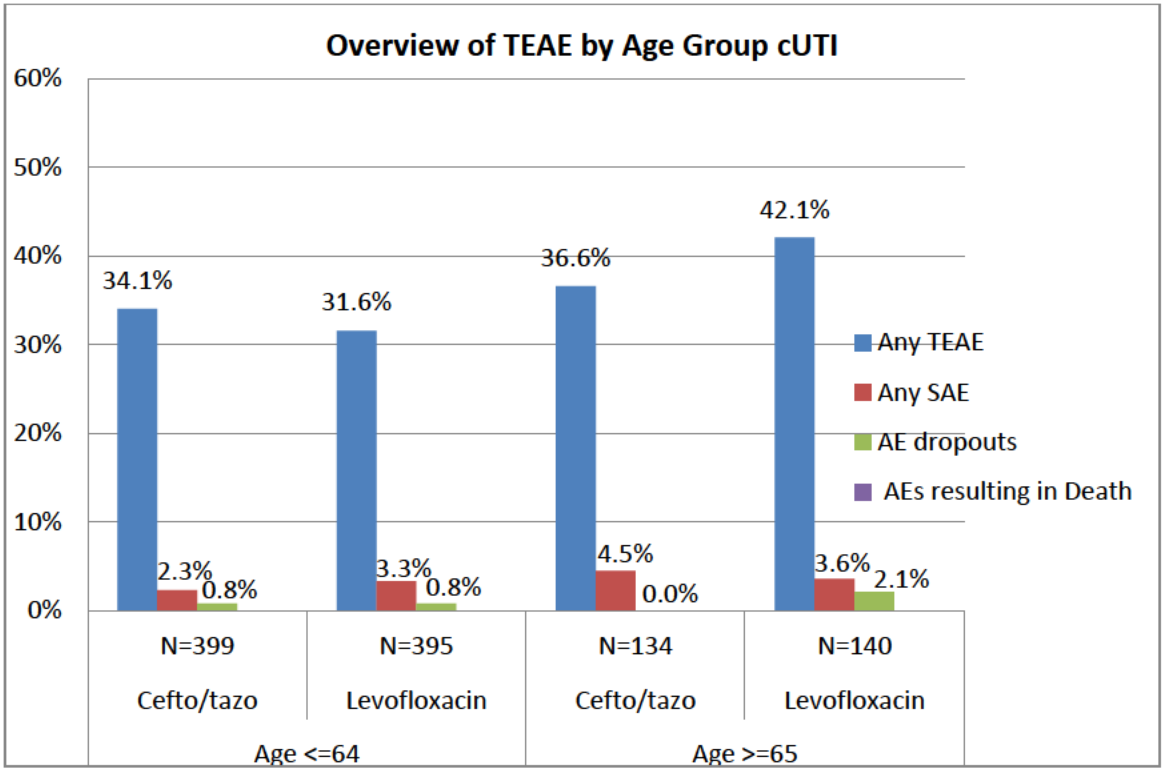
7.5.2 Time Dependency for Adverse Events

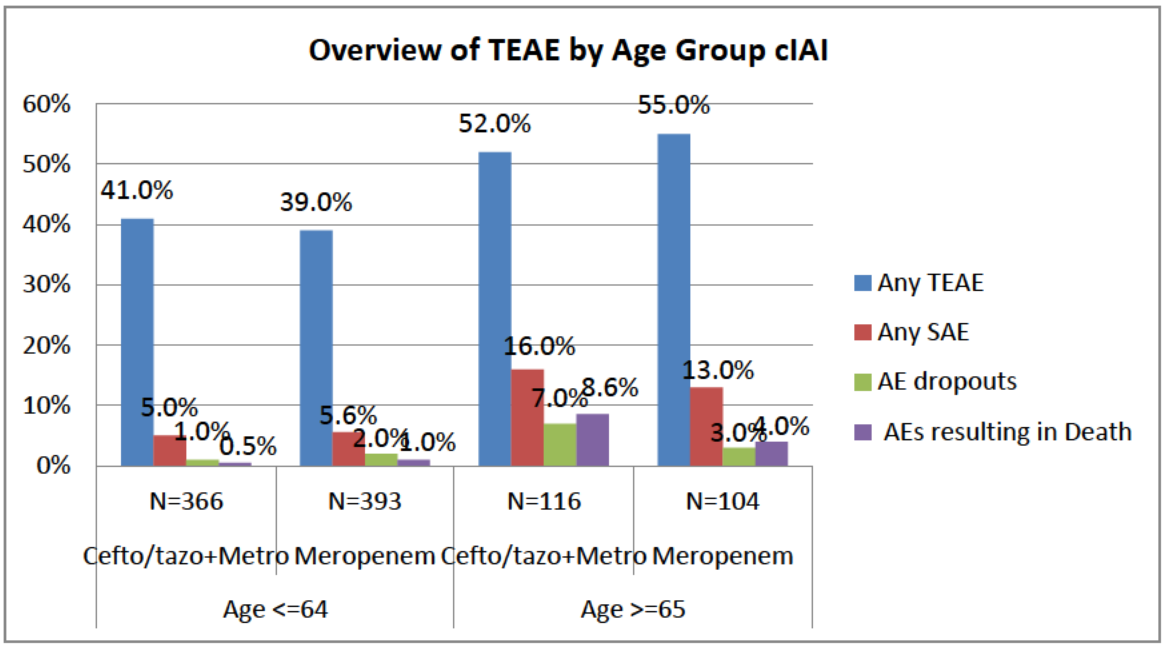
No clear time dependency was observed for adverse events.

7.5.3 Drug-Demographic Interactions

Overall, the distribution of AEs among the age cohorts was characterized by an increased frequency of AEs in the older populations in both Phase 3 studies, with a tendency towards a higher frequency of SAEs in the older patients in the cIAI study. The graph below shows a distribution of AEs by frequency and severity (SAEs and fatal AEs) across both Phase 3 trials for cUTI and cIAI.

Figure 5: Treatment emergent adverse events by Age in Phase 3 trials





7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

Please refer to the Dr. Ryan Owen's review of clinical pharmacology.

7.6 Additional Safety Evaluations

Not applicable

7.6.1 Human Carcinogenicity

Please refer to Section 4.3.

7.6.2 Human Reproduction and Pregnancy Data

Please refer to Dr. James Wild's pharmacology-toxicology review.

7.6.3 Pediatrics and Assessment of Effects on Growth

In accordance with Section 505(B)(a)(3)(A)(ii) of the PREA, Cubist requested a deferral of planned pediatric studies until safety and efficacy of ceftolozane/tazobactam is established in the adult population. The Division, with concurrence from the Pediatric Review Committee, agreed to the initial Pediatric Study Plan submitted by the applicant on September 18, 2013.
Cubist will conduct three clinical trials in children aged 0 to 17 years to support the use of ceftolozane/tazobactam in the indications of cUTI and cIAI in pediatric subjects.
Each of the three clinical trials proposed in the pediatric development program would contain the following cohorts and sub-groups as follows:

(b) (4)

The first study will assess the safety and pharmacokinetics (PK) of several doses of ceftolozane/tazobactam in children (b) (4) within 0-17 years of age) to support a dose selection for cIAI and cUTI proposed pediatric clinical safety and efficacy studies. Two randomized and active controlled clinical trials, one in cUTI and one in cIAI, will be conducted in children ages 0 to 17 years. (b) (4) . The dose and frequency of administration will be selected upon review of the data from the pediatric PK trial.

The table below outlines agreed upon timelines for the pediatric development program.

Table 68: Pediatric Development Program timelines

Study 1: A single dose, multicenter, non-comparative study to assess the PK of ceftolozane/tazobactam in pediatric patients ages 0 to <18 years	
Protocol Submission Date:	February 26, 2014
Estimated Study Initiation Date:	June 2014
Estimated Final Study Report Submission Date:	December 2016
Study 2: A randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cUTI	
Estimated Protocol Submission Date:	April 2017
Estimated Study Initiation Date:	June 2017
Estimated Final Study Report Submission Date:	December 2020
Study 3: A randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cIAI	
Estimated Protocol Submission Date:	April 2017
Estimated Study Initiation Date:	June 2017
Estimated Final Study Report Submission Date:	December 2020

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

7.7 Additional Submissions / Safety Issues

The applicant submitted a 120-day clinical and preclinical safety update on August 20, 2014, to NDA 206829, SDN 019. For the preclinical update, containing results from the pivotal 28-day GLP juvenile rat toxicity study outlined in the Pediatric Study Plan (PSP), please refer to Dr. James Wild's pharmacology-toxicology review.

The clinical safety update summarizes information obtained during the reporting period from October 15, 2013 (last patient, last visit (LPLV), for any of the pivotal Phase 3 studies included in the NDA) to the cutoff date of June 21, 2014.

Two studies were ongoing during the reporting period of 15 October 2013 to 21 June 2014: the non-pivotal nosocomial pneumonia trial, CXA-NP-11-08, entitled "A Multicenter, Open-Label, Randomized Study to Compare the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam with that of Piperacillin/Tazobactam in Ventilator Associated Pneumonia", and CXA-EB-13-05,

entitled "A Single-Dose, Open-Label, Parallel-Group Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ceftolozane/Tazobactam Administered Intravenously to Adult Japanese, Chinese and Caucasian Healthy Subjects" (Protocol Version 1 was submitted on 20 December 2013 (IND Sequence No.0159). There were no IND safety reports submitted during the reporting period. A total of 21 subjects has been enrolled in this study as of the cutoff date of June 21, 2014. One subject, Subject 001-1001, a 26-year-old Chinese female, discontinued study participation after the non- serious adverse event of acute drug eruption. On 29 June 2014 the subject received a single dose of 1.5 g ceftolozane/tazobactam intravenously. On 01 July 2014 the subject experienced the AE of acute drug eruption, which was mild in severity and assessed as related to ceftolozane/tazobactam. On 05 July 2014 the event was resolved. The subject withdrew from the study on 09 July 2014.

CXA-NP-11-08 study update

Four patients were enrolled in Study CXA-NP-11-08, which evaluated ceftolozane/tazobactam at a dose of 3.0 g IV every 8 hours, comprising 2.0 g of ceftolozane and 1 g of tazobactam, versus piperacillin/tazobactam (4.5 g IV every 6 hours, comprising 4 g piperacillin and 500 mg tazobactam) in the treatment of hospital-acquired bacterial pneumonia or hospital-acquired ventilator associated pneumonia (HABP/HAVP) patients.

On December 31, 2013, the applicant electively discontinued the study [redacted] (b) (4) the pivotal safety and efficacy study for the HABP/HAVP indication, CXA-NP-11-04, which will compare ceftolozane/tazobactam to meropenem and will include all recent recommendations provided by our Division.

An abbreviated clinical study report was submitted to IND 104,490 on August 12, 2014, SDN 183. The protocol was open for enrollment since July 3, 2013. From a total of 19 sites, three sites enrolled a total of 4 patients up to December 8, 2013. Two of these sites were in the United States and 1 site in Australia (three subjects were enrolled in the United States and 1 subject in Australia). Of the four patients enrolled:

- 1 subject, (Subject No. 55020-00015), randomized to ceftolozane/tazobactam, prematurely discontinued due to withdrawal of consent.

- 2 subjects experienced SAEs (Subject 55015-0001, a ceftolozane/tazobactam-treated subject, experienced acute physical deterioration (assessed by the investigator as recovered/not related) and diffuse bowel ischemia (fatal/not related) and Subject 11003-00001, a piperacillin/tazobactam-treated subject, experienced ventriculitis, assessed as not related to study drug.

- 1 subject experienced no AEs (a piperacillin/tazobactam-treated subject; Subject No.55020-00106).

Except for the patient who discontinued prematurely, all three patients received the protocol-specified 8 days of study therapy.

Summary narratives of ceftolozane/tazobactam patients

Subject 55020-00015, a 68 year old White male from the United States, randomized to the ceftolozane/tazobactam received ceftolozane/tazobactam 3 g IV q8h from 03 July 2013 to 05 July 2013. Criteria for hospital-acquired pneumonia were met with radiological signs and a lower respiratory tract culture by mini-bronchoalveolar lavage (BAL) showing growth of *Enterobacter aerogenes* and *Morganella morganii*, both sensitive to ceftolozane/tazobactam

On 05 July 2013 (study day 3), a chest x-ray revealed worsening progressive diffuse/patchy infiltrates of the right lower and left lower zones. The same date, the subject experienced a non-serious AE of a urinary tract infection deemed not related to study therapy by the Investigator. The subject's wife subsequently withdrew consent from further participation in the study. The subject was started on non-study antibiotics. The final dose of study drug was taken on 05 July 2013 (study day 3). The urinary tract infection AE recovered/resolved on 09 July 2013.

Medical Reviewer's comment: the progression of infiltrates during treatment raises the possibility of treatment failure due to a new or worsening pulmonary infection, which cannot be ruled out. The drug exposure (approximately 48 hours) was short before consent was withdrawn.

Subject 55015-0001, a 56 year old white male with history of hypertension, diabetes mellitus, alcoholism and tobacco use and cardiomyopathy, from the United States, was randomized to the ceftolozane/tazobactam treatment group. The subject received ceftolozane/tazobactam 3 g IV q8h from study day 1 to study day 8.

Criteria for hospital-acquired pneumonia were confirmed with CT scan and a lower respiratory tract culture by BAL showing growth of *Klebsiella pneumoniae* and *Streptococcus viridans* Both organisms were sensitive to ceftolozane/tazobactam Blood cultures were negative for growth. The subject began study drug administration the same date, along with concomitant administration of linezolid 600 mg IV q12h as required per protocol.

On study day 3, a lower respiratory tract culture by BAL showed growth of *Pseudomonas aeruginosa*, sensitive to ceftolozane/tazobactam, and a chest x-ray revealed unchanged localized/dense infiltrates of left lower zone and improvement in the right lower zone. The Clinical Pulmonary Infection score was 8, and the Sepsis-related Organ Failure Assessment score remained at 6.

Between study days 4-10, chest x-rays continued to show an infiltrates of the left and right lung bases. During this same timeframe, the subject started to show signs of metabolic acidosis. On study day 8, the subject received the final dose of study medication. On the same date at the EOT visit, a lower respiratory tract culture by BAL showed growth of *Acinetobacter baumannii* (at 2 x10^2 CFU/mL, resistant to ceftolozane/tazobactam with an MIC of ≥256), and a chest x-ray revealed unchanged localized/dense infiltrates of the right lower and left lower zones from baseline. Clinical Pulmonary Infection (CPIS) score was 10, and the Sepsis-related Organ Failure Assessment score was 7. The Investigator assigned the subject a clinical response of

'indeterminate', as the EOT cultures revealed a new organism, different from the baseline pathogen. Also on study day 8, the subject experienced the life-threatening SAE of acute physical deterioration requiring re-intubation.

On [redacted] (b) (6) (study day 9), the day after study medication was discontinued, a repeat bronchial culture revealed Gram-negative rods (identification not provided by the applicant). A chest x-ray revealed improved aeration of the right lung base and persistent retrocardiac left basilar pneumonia. A chest CT and a CT of the abdomen and pelvis (both without contrast) both revealed findings suggestive of bowel ischemia/infarction.

The CT of the abdomen and pelvis also showed dilated loops of large and small bowel with extensive pneumatosis intestinalis in the small and the large bowel. Heterogeneous attenuation of the kidneys suggested vascular compromise and ischemia. The subject was consequently diagnosed with a life-threatening SAE of diffuse bowel ischemia, which was deemed not related to study drug by the Investigator. The CT of the chest also revealed progression of consolidation and pneumonic infiltrate in the left lower lobe as compared to previous examination with a small left-sided pleural effusion. The same day, the subject developed hypotension and tachycardia, without response to normal saline bolus and vasopressor support. . The subject became hypotensive and bradycardic and subsequently died the same day as a result of the diffuse bowel ischemia SAE.

Medical Reviewer's comment: the worsening CPIS and SOFA scores and acute physical deterioration requiring re-intubation, in addition to the presence of a new organism (Acinetobacter baumannii) from a BAL after four days of treatment strongly suggests the possibility of treatment failure instead of an "indeterminate" outcome. This subject was at high risk when enrolled, based on a CPIS score of 10. The fatal SAE of bowel ischemia may have been caused by severe and prolonged hypotension in the setting of underlying predisposing conditions (diabetes, hypertension, and cardiomyopathy).

Safety Update Conclusions

CXA-NP-11-08 study: These are the first two patients to receive ceftolozane/tazobactam at a dose of 3 g IV Q 8 hours. One of the subjects completed the full 8-day treatment and died from bowel ischemia on Day 8, judged unrelated to study drug. The other subject withdrew consent from the study after 48 hours of treatment, while worsening pulmonary infiltrates and a urinary tract infection were observed.

The 3g dose (2g of ceftolozane and 1 g of tazobactam) has been tested in a total of 8 healthy volunteers, one of whom withdrew prematurely from the study because of adverse events (vomiting after the second dose). Only one subject has received a dose higher than 3 g. In the CXA-QT-10-02 study, the only subject who received both the therapeutic and a supratherapeutic dose of ceftolozane/tazobactam (4.5 g) discontinued the study due to pyrexia. The event occurred after the subject had received both the 1.5 g therapeutic and 4.5 g supra-therapeutic doses of ceftolozane/tazobactam on Days 1 and 5, respectively.

The currently available data with ceftolozane/tazobactam at 3g IV Q 8 hours or higher is extremely limited and no conclusions can be made yet about the safety or efficacy of this dose, when given as a treatment regimen or accidentally received as an overdose. More data will be needed before this dose can be recommended for this or any other indication.

CXA-EB-13-05 study: A Chinese female withdrew from the study due to an adverse event of acute drug eruption, which occurred after the first dose and was mild and resolved. Rash has been observed at a rate lower than 2% in ceftolozane/tazobactam studies. It is unclear which kind of drug eruption this patient had and more information will be requested from the applicant. Since the event was mild and resolved after drug discontinuation, no changes to the study conduct are warranted.

8 Postmarket Experience

None

9 Appendices

Appendix 1

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 206829

Submission Date(s): April 21, 2014

Applicant: Cubist Pharmaceuticals, Inc.

Product: Ceftolozane/tazobactam

Reviewer: Maria Allende, M.D.

Date of Review: September 19, 2014

Covered Clinical Study (Name and/or Number): CXA-10-04-10-05 and CXA-10-08-10-09

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 420		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 (one)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 1 (one) investigator Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 (none)		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Investigator Name	(b) (6)
Site Number	
Site Name	
Principal Investigator	

(b) (6) was a participating sub-investigator in Study CXA-cIAI-10-08: *A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Efficacy and Safety of Intravenous CXA-201 with that of Meropenem in Complicated Intraabdominal Infections.* (b) (6) reported a financial interest to Cubist via Financial Disclosure Forms dated 29Aug11, 21Nov11, and 01Apr13. He confirmed by checking Yes on each form that the nature of the interest is "ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria (>$25,000 cumulatively)." The site was contacted by the applicant for further details, and it was reported by the site that (b) (6) was paid by Cubist for speaking engagements.

The multi-site nature of CXA-cIAI-10-08 and CXA-cIAI-10-09 helped to minimize the potential for bias coming from any individual sites. In addition, Site (b) (6) enrolled 7 subjects out of 993 patients (fewer than 1% of patients) across the CXA-cIAI-10-08 and CXA-cIAI-10-09 trials. The site was closed early due to investigator non-compliance, and data from this site were excluded from efficacy analysis.

1 See [web address].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIA C ALLENDE
10/22/2014

THOMAS D SMITH
10/22/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206829 **Applicant: Cubist, Inc.** **Stamp Date: April 21, 2014**

Drug Name: Ceftolozane/tazobactam (ZERBAXA®) **NDA Type: 505 (b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?				
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Piperacillin-tazobactam (Zosyn®)
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	The applicant has conducted preclinical studies with their own manufactured product.
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	The applicant has conducted preclinical studies with their own manufactured product; no bridging studies were requested. The applicant has also obtained additional information from published literature and from the piperacillin-tazobactam (Zosyn®) label.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:		X		The applicant has not conducted dose ranging studies, which were recommended by the Division; however, their database includes several PK and safety studies to support dosing in subpopulations with renal impairment. This may be a review issue.
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 CXA-10-04-10-05 Indication: cUTI Pivotal Study #2 CXA-10-08-10-09 Indication: cIAI	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			The applicant submitted a brief statement explaining the use of foreign data. For this class of drug and indication, there are no known differences previously identified regarding its use in the US as compared with other populations. Some issues may be identified during the review.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?				
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			The applicant submitted a brief statement explaining the use of foreign data. For this class of drug and indication, there are no known differences previously identified regarding its use in the US as compared with other populations. Some issues may be identified during the review process.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	reasonable review of the patient data?				
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIA C ALLENDE
06/16/2014

THOMAS D SMITH
06/16/2014