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STATISTICAL REVIEW(S)

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Center for Drug Evaluation and Research

Office of Translational Sciences

Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	206829
Drug Name:	Ceftolozane/tazobactam (Zerbaxa) for Injection
Indication:	Complicated Intra-abdominal Infections
Applicant:	Cubist Pharmaceuticals
Stamp Date:	April 21, 2014
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1. EXECUTIVE SUMMARY

This submission provided adequate evidence of efficacy and safety for Zerbaxa™ (ceftolozane/tazobactam) administered as an i.v. treatment (1.5g every 8 hours [redacted] (b) (4)) in adult patients with complicated intra-abdominal infections (cIAI). However, overall evidence was not considered to be highly robust since it relied on a single Phase 3 pivotal trial (Trial cIAI-10-08&09 hereafter referred to as Trial -08&09) which only narrowly met its primary objective of demonstrating the non-inferiority of ceftolozane/tazobactam + metronidazole to comparator therapy (i.v. meropenem) using a pre-specified margin of 10%.

In Trial -08&09, the primary analysis of clinical cure rates at the Test-of-Cure (TOC) visit on Day 24-32 was performed in the Microbiological Intent-to-treat (MITT) population which is based on all randomized patients with at least 1 baseline intra-abdominal pathogen regardless of susceptibility to study drug. The primary analysis showed lower rates in the ceftolozane/tazobactam + metronidazole arm than in the meropenem arm at 323/389 (83.0%) vs. 364/417 (87.3%), a treatment difference of -4.3% (95% CI: -9.2%, 0.7%), **Table 6**. This finding satisfied the pre-specified non-inferiority hypothesis based on a 10% NI margin with a lower confidence limit of -9.2% which fell slightly above the minimum requirement for non-inferiority at -10%. Treatment differences were negatively impacted by a larger percentage of ceftolozane/tazobactam + metronidazole patients who were counted as failures due to indeterminate outcomes, 34/389 (8.7%) vs. 19/417 (4.6%).

The Reviewer's post-hoc sensitivity analyses consistently showed less favorable treatment differences in the ceftolozane/tazobactam + metronidazole arm. However, differences were less pronounced than in the primary analysis and were still supportive of non-inferiority, **Section 4.1**. These sensitivity analyses considered a broad range of conditions, including various analysis populations, timings of assessment, stratification factors and re-classifications of the primary assessment (e.g. due to surgical review panel (SRP) assessment, unplanned surgeries, use of concomitant antibiotics).

The Reviewer's subgroup analyses based on prognostic variables of interest also showed less favorable findings across most subgroups. In addition, these analyses showed a possible trend towards less favorable treatment comparisons in ceftolozane/tazobactam + metronidazole patients with higher risk profiles at baseline (e.g. age ≥ 65 years, region of N.America/W.Europe/Rest of World, primary site of infection of bowel, anatomic site of infection of non-appendix, prior antibiotic use, APACHE II Score > 10, creatinine clearance < 50 mL/min. or multiple abscesses), **Section 5**.

As a post-marketing commitment, the Reviewer recommends that the Applicant conducts an additional adequate and well controlled study in higher risk patients with substantially lower expected clinical cure rates (e.g. patients with creatinine clearance < 50 mL/min).

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2. INTRODUCTION

2.1 Overview

Background

In this 505(b)(2) NDA submission, Cubist Pharmaceuticals is seeking approval of Zerbaxa™ for the treatment of complicated abdominal infections in adult patients. To support the efficacy and safety of Zerbaxa, Cubist has submitted results from a Phase 3 randomized, double-blind, double-dummy, multi-center trial (Trial -08&09) as well as a randomized double-blind Phase 2 trial (Trial CXA-IAI-10-01 hereafter referred to as Trial -01). These trials are described below in **Table 1**.

Originally, Cubist initiated 2 identical Phase 3 trials, each with a planned sample size of 906 subjects (453 subjects per arm). However, based on the release of the FDA Draft Guidance for cIAI[1] and subsequent discussions with the Division, Cubist switched to a single study strategy for the cIAI indication. Such a strategy was achieved by pooling subjects from the two ongoing Phase 3 trial protocols into a single Phase 3 trial (Trial -08&09). Trial -08&09 enrolled 993 subjects, 487 subjects in the ceftolozane/tazobactam + metronidazole arm and 506 in the meropenem arm.

In Trial -08&09, the primary objective was to establish the non-inferiority of ceftolozane/tazobactam + metronidazole to meropenem in adult subjects with cIAI based on the proportion of subjects who achieved clinical cure at the TOC visit in the MITT population. In order to show non-inferiority within 10% (the pre-specified NI margin) in the primary analysis, the lower 95% confidence limit for the treatment difference in clinical cure rates (ceftolozane/tazobactam + metronidazole minus meropenem) had to be at least -10%.

Submitted Studies

A brief overview of the two cIAI trials is provided in **Table 1**. This review primarily considers findings from Trial -08&09 due to the various limitations with the Trial -01 design. For example, Trial -01 considered study therapy over a duration of 4-7 days vs. 4-10 days in Trial -08&09 and a timing of the primary assessment at 7-14 days post-therapy vs. 24-32 days post-therapy in Trial -08&09. Trial -01 was also limited by unfavorable treatment comparisons and small sample sizes (Appendix, **Table 25**).

Table 1: Description of cIAI Trials: Trial -01 and Trial -08&09

	Description of Trial
Trial -01	Phase 2, multicenter, prospective, randomized, double-blind comparative efficacy and safety trial of ceftolozane/tazobactam, (1.5 g every 8 hours) plus metronidazole (500 mg every 8 hours) administered as an IV infusion versus meropenem (1 g every 8 hours) and a matching saline placebo (every 8 hours) administered as an IV infusion in the treatment of adult subjects with cIAI.

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Trial -08&-09	Phase 3, multicenter, prospective, randomized, double-blind, placebo dummy trial of ceftolozane/tazobactam (1.5 g every 8 hours) plus metronidazole (500 mg every 8 hours) administered as an IV infusion versus meropenem (1 g every 8 hours) and placebo (every 8 hours) administered as an IV infusion in the treatment of adult subjects with cIAI requiring surgical intervention.

Source: Reviewer Table

2.2 Data Sources

The reviewer primarily considered the clinical summary of efficacy, clinical study reports and selected datasets which are described below for Trial -08&09 along with their links. Datasets in Trial -08&09 were adequate in terms of their structure and naming conventions. The data formats used in this submission were SDTM and ADAM.

- Clinical Summary of Efficacy & Safety : \\cdsesub1\evsprod\NDA206829\0001\\m2\27-clin-sum
- Clinical Study Report: \\Cdsesub1\evsprod\NDA206829\0001\m5\53-clin-stud-rep
- Datasets: \\Cdsesub1\evsprod\NDA206829\0001\m5\datasets\cxa-ciai-10-08-10-09\analysis\adam\datasets
    - ADAE- Adverse Events
    - ADCM- Prior and Concomitant Medications
    - ADMB- Microbiology
    - ADSL- Subject Level Analysis Dataset
    - ADXO- Clinical Outcomes

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the data quality was acceptable. No errors were noted in any of the submitted datasets. Datasets and variables were clearly described and well-documented. The Reviewer could reproduce all major analyses.

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3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

Treatment Arms: Subjects were randomly assigned to receive either ceftolozane/tazobactam + metronidazole or comparator therapy (meropenem and placebo) in a 1:1 randomization ratio by using an interactive voice response system/interactive web response system (IVRS/IWRS). Randomization was stratified by investigational site and primary site of infection with 2 levels: 'bowel (small or large)' versus 'other site'. Subjects with appendix, stomach, or duodenum as the anatomic site of infection, were stratified to the 'other site' group during the randomization process. Complicated appendicitis was further classified as generalized (e.g. diffuse peritonitis) or localized. The number of subjects with localized complicated appendicitis was limited to approximately 30% of the randomized population.

Design: This was a multicenter, prospective, randomized, double-blind, placebo dummy, Phase 3 study of ceftolozane/tazobactam (1.5 g every 8 hours) and metronidazole (500 mg every 8 hours) administered as an intravenous (IV) infusion versus meropenem (1 g every 8 hours) and placebo administered as an IV infusion in the treatment of adult subjects with cIAI requiring surgical intervention. This study was designed to determine the clinical and microbiological response to treatment with ceftolozane/tazobactam as well as to assess the safety.

As shown in **Figure 1**, subjects participated in three phases: Screening (Baseline, Day -1 to Day 1 before dosing), Treatment (Day 1 to Day 10) and Post Treatment (EOT visit within 24 hours after the last dose of study drug, TOC visit 24 to 32 days after the first dose of study drug, and LFU visit 38 to 45 days after the first dose of study drug). The total duration of study drug administration (IV only) was 4 to 10 days. Subjects received study drug for up to 14 days if they did not meet study drug discontinuation criteria by Study Day 10. Subject participation required a minimum commitment of 38 days and a maximum of 45 days. The actual duration of the study was 22 months.

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Figure 1: Overall Study Design, Trial-08&09

Screening	On Treatment	End-of-Therapy (EOT)	Test-of-Cure (TOC)	Late Follow-up (LFU)
Day -1 to Day 1	Day 1 to Day 10	Within 24 hrs. of last dose of study drug	24-32 days after first dose of study drug	38 to 45 days after first dose of study drug
Establish diagnosis of cIAI Baseline screening assessments Obtain baseline intra-abdominal and blood specimens for culture Randomize 1:1 to treatment	IV 60-min. infusions over 8 hrs ceftolozane/tazobactam (1.5 g q8h) and metronidazole (500 mg q8h) OR meropenem (1 g q8h) and matching placebo Assessment for cIAI symptoms and AEs Total duration of study therapy is 4 to 10 days[1]	Assessments for microbiological response, clinical response, and safety	Return to study center for primary assessments of microbiological response and safety	Return to study center for final assessments of microbiological response, clinical response, and safety

[1] Some subjects could receive up to 14 days of study drug if discontinuation criteria were not met by Study Day 10
Source: Reviewer Figure

Reviewer Comments: *All subsequent tables and figures in this review refer to the MITT Population of Trial -08&09 unless otherwise stated.*

The Reviewer's description of the Applicant's inclusion and exclusion criteria are shown below:

Inclusion Criteria

1. Patient must give informed consent.
2. Male or female patients ≥ 18 years of age.
3. If female, subject was nonlactating, and was either not of child bearing potention or of child bearing potential and practiced reliable birth control methods during conduct of study and at least 35 days after last dose of study medication.
4. Male patients were required to practice reliable birth control methods during conduct of study and at least 35 days after last dose of study medication.
5. Had 1 of the following diagnoses (in which there was 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 peri-appendiceal abscess;
   d. Acute gastric or duodenal perforation, only if operated on > 24 hours after perforation;

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e. Traumatic perforation of the intestine, only if operated on > 12 hours after perforation;
f. Peritonitis due to other perforated viscus or following a prior operative procedure;
g. Subjects with inflammatory bowel disease or ischemic bowel disease were eligible provided there was bowel perforation.
h. Intra-abdominal abscess (including liver or spleen).

6. The subject required surgical intervention (eg, laparotomy, laparoscopic surgery, or percutaneous draining of an abscess) within 24 hours of (before or after) the first dose of study drug.
7. If a subject was enrolled preoperatively, the subject had radiographic evidence of bowel perforation or intra-abdominal abscess.
8. Subjects who failed prior antibacterial treatment for the current cIAI were enrolled but must have had: (a) a positive culture (from an intra-abdominal site) and (b) required surgical intervention. Such subjects were enrolled before the results of the culture were known; however, if the culture was negative, study drug administration must have been discontinued.
9. Willingness and ability 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°Celsius (C) or less than 35°C;
    b. Elevated white blood cells (WBC; >10 500/mm^3);
    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, pre-operative enrollment and dosing is acceptable, provided that the sample from the site of infection is obtained during the interventional procedure).

Exclusion Criteria

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 intra-abdominal infection managed by staged abdominal repair (STAR), open abdomen technique (ie, fascia not closed) including temporary closure of the abdomen, or any situation where infection source control was not likely to be achieved.
5. Known to have an IAI or postoperative infection caused by pathogen(s) resistant to meropenem prior to randomization.
6. Use of systemic antibiotic therapy for IAI for more than 24 hours prior to the first dose of study drug, unless there was a documented treatment failure with such therapy.
7. More than 1 dose of an active non-study antibacterial regimen given postoperatively. For subjects enrolled preoperatively, no postoperative non-study antibacterial therapy was allowed.
8. Subjects who previously received imipenem, meropenem, doripenem, or cefepime for the current intra-abdominal infection.

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9. Had a concomitant infection at the time of randomization, which required non-study systemic antibacterial therapy in addition to IV study drug therapy. Drugs with only Gram-positive activity (eg, daptomycin, vancomycin, linezolid) were allowed.
10. Severe impairment of renal function (estimated CLCR <30 mL/min), or requirement for peritoneal dialysis, hemodialysis or hemofiltration, or oliguria.
11. The presence of hepatic disease at baseline was defined by any of the following:
    a. ALT (SGPT) or AST (SGOT) > 4 × upper limit of normal (ULN)
    b. Total bilirubin >2 ULN, unrelated to cholecystitis
    c. Alkaline phosphatase (ALP) > 4 × ULN. Subjects with a value >4 × ULN and <5 × ULN were eligible if this value was historically stable.
    d. Acute or chronic hepatitis, cirrhosis, acute hepatic failure, acute decompensation of chronic hepatic failure.
12. Hematocrit <25% or hemoglobin <8 g/dL.
13. Neutropenia with absolute neutrophil count <1000/mm^3.
14. Platelet count <75 000/mm^3. Subjects with a platelet count as low as 50 000/mm^3 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, 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. Had a documented history of any moderate or severe hypersensitivity or allergic reaction to any beta-lactam (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 ceftolozane or ceftolozane/tazobactam.
22. Subjects who received disulfiram in the past 14 days or who were currently receiving probenecid.
23. Women who were pregnant or nursing.

Analysis Populations: The Applicant pre-specified the following analysis populations in Trial - 08&09. Definitions for these populations (as summarized by the Reviewer) are shown below:

- **Intent-to-Treat (ITT) Population**- All randomized patients.
- **Safety Population**- ITT patients who received at least 1 dose of (active) study drug.

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- **MITT Population (Primary Analysis Population)-** ITT patients who had IAI as evidenced by identification of at least 1 baseline intra-abdominal pathogen, regardless of susceptibility to study drug.
- **Clinically Evaluable (CE) Population-** ITT patients who received an adequate amount of study drug, met the protocol-specific disease definition of cIAI, adhered to study procedures, and had a TOC visit within the specified visit window.
- **ME Population-** CE subjects who had at least 1 baseline infecting pathogen identified that was susceptible to study drug.
- **Expanded ME Population-** Subjects who had a baseline infecting IAI pathogen, regardless of susceptibility to study drug, and met CE criteria.
- **CE at Late Follow-up (LFU) Population-** CE subjects who were clinical cures at the TOC visit and had an LFU assessment.
- **ME at LFU Population-** ME subjects who were clinical cures at the TOC visit and had an LFU assessment.

Reviewer Comments: The *Reviewer mainly considered the Applicant's pre-specified primary analysis population (i.e. the MITT population) in analyses of efficacy (clinical and microbiological analyses) and the Safety Population in analyses related to safety.*

Sample Size Determination: Assuming a 1-sided alpha of 0.025, a 10% NI margin, 75% clinical response rate in both treatment arms, 80% evaluability rate, and 90% power, the final sample size of the study was planned to be 988 patients (494 per arm) resulting in an estimated 395 MITT patients per arm.

Study Endpoints

Primary Efficacy Outcome Measure: The primary efficacy variable was the clinical cure rate in the MITT population at the TOC visit. The Investigator classified clinical response at the EOT and TOC visits as 'clinical cure', 'clinical failure', or 'indeterminate' based on the clinical outcome. Failure was carried forward; subjects who were assessed as a failure prior to the TOC visit had "failure" recorded on the TOC outcome visit of the eCRF. Definitions for the clinical outcomes are shown in **Table 2**.

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Table 2: Clinical Response Definitions at the EOT and TOC Visits (Trial -08&09)

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 or drainage procedure was 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.[1] • Need for treatment with additional antibiotics for ongoing symptoms of IAI prior to the TOC, or • Postsurgical wound infection, defined as an open wound with signs of local infection, such as purulent exudate, erythema, or warmth that required additional antimicrobial therapy and/or non-routine wound care (such as incision and drainage or re-opening of the wound).[2] Note: Closure of a colostomy or an enterocutaneous fistula was not considered a failure. Wherever possible, failures were documented microbiologically by obtaining an appropriate deep wound or intra-abdominal site culture. Blood cultures should also have been obtained.
Indeterminate	• Study data were 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 classification as cure or failure (e.g. subject lost to follow-up).

[1] Repeat percutaneous aspiration of an abscess within 72 hours of the original aspiration, without worsening clinical signs and symptoms, was not considered a failure. However, the need to repeat any procedure after 72 hours of study therapy to cure the infection was considered a failure. Exploratory or diagnostic procedures with no evidence of an ongoing infection were not considered a failure.
[2] Use of vacuum-assisted wound closure following fascial closure was acceptable and such procedure was reported on the abdominal intervention page. Daily wound assessments were conducted according to the Schedule of Assessments.
Source: Table 6 of the Applicant's CSR

Secondary Efficacy Outcome Measure: The Applicant also pre-specified a secondary endpoint which was the clinical cure rate at the TOC visit in the ME population. Other secondary efficacy variables included:

- Clinical cure rates at the TOC visit in the CE Population.
- Per-subject microbiological success rates at the TOC visit.
- Per-pathogen microbiological response rates at the TOC visit.
- The proportions of subjects with superinfections or new infections.
- Clinical cure rates at the EOT and LFU visits.
    - Clinical cure rates at the TOC visit for subjects infected with an ESBL-producing organism at baseline.
    - Per-pathogen microbiological response rates at the TOC visit in subjects infected with an ESBL-producing organism at baseline.
    - Per-pathogen clinical cures rate at the TOC visit by baseline minimum inhibitory concentration (MIC).

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3.2.2 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

There were 993 randomized subjects (487 patients in the ceftolozane/tazobactam + metronidazole arm and 506 in the meropenem arm) with 928 (93.5%) of all randomized subjects completing the trial. As shown in **Table 3**, the primary analysis population (MITT) included 806 patients with 761 (94.4%) of subjects completing the trial. There were more subjects in the ceftolozane/tazobactam + metronidazole than in the meropenem arm who withdrew from the study at 26 (6.7%) vs. 19 (4.6%) and who prematurely discontinued study drug at 27 (6.9%) vs. 24 (5.8%).

Table 3: Disposition of Subjects in Trial -08&09 (MITT Population)

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	1 (0.1)
Patient's Decision	9 (2.3)	6 (1.4)	15 (1.9)
Other	1 (0.3)	4 (1.0)	5 (0.6)

[1] 11/11 (100%) of ceftolozane/tazobactam + metronidazole & 6/7 (86%) of meropenem patients with AE had a death.
[2] 6/12 (50%) of ceftolozane/tazobactam + metronidazole & 3/11 (27%) of meropenem patients with AE had a death.
Source: Reviewer Table

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Table 4 shows the number (%) of patients by analysis population in Trial -08&09. There were fewer subjects in the ceftolozane/tazobactam + metronidazole arm than in the meropenem arm for each of the analysis populations. The ceftolozane/tazobactam + metronidazole arm included a smaller percentage of ITT patients in most of the analysis populations, especially in the ME based populations. However, the percentage of ITT patients in the Safety population was slightly higher in the ceftolozane/tazobactam + metronidazole arm at 482/487 (99.0%) vs. 497/506 (98.2%).

Table 4: Number (%) of Patients by Analysis Population

Analysis Population	Ceftolozane/ Tazobactam + Metronidazole n (%)	Meropenem n (%)	Total n (%)
ITT	487 (100)	506 (100)	993 (100)
Safety	482 (99.0)	497 (98.2)	979 (98.6)
MITT[1]	389 (79.9)	417 (82.4)	806 (81.2)
CE	375 (77.0)	399 (78.9)	774 (77.9)
ME	275 (56.5)	321 (63.4)	596 (60.0)
Expanded ME	307 (63.0)	345 (68.2)	652 (65.7)
CE at LFU	350 (71.9)	374 (73.9)	724 (72.9)
ME at LFU	258 (53.0)	304 (60.1)	562 (56.6)

[1]Primary analysis population was the MITT
Source: Reviewer Table

Prognostic Factors at Baseline

Prognostic factors at baseline in the primary analysis population of Trial -08&09 were generally similar between treatments, as shown in **Table 5**. However, there was a slightly higher percentage of ceftolozane /tazobactam + metronidazole patients who were 65 years of age or older, female, with creatinine clearance < 50 mL/min, with APACHE II Scores ≥ 10, with peritonitis, with an anatomic site of infection of non-appendix or with a laparotomy procedure. A slightly lower percentage of ceftolozane/tazobactam + metronidazole patients originating from Western Europe or receiving a percutaneous aspiration procedure at baseline was also noted.

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Table 5: Number (%) of Patients with Prognostic Factors at Baseline by Treatment (MITT)

Statistic/Category	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Total (N=806) n (%)
Age (Years)			
Mean (Std. dev.)	50.8 (18.3)	50.4 (16.9)	50.6 (17.5)
Median (Min, Max)	51 (18, 92)	52 (18, 92)	52 (18, 92)
Age group			
≥18 to <65	289 (74.3)	332 (79.6)	621 (77.0)
≥ 65	100 (25.7)	85 (20.4)	185 (23.0)
≥ 75	46 (11.8)	37 (8.9)	83 (10.3)
Gender			
Male	218 (56.0)	248 (59.5)	466 (57.8)
Female	171 (44.0)	169 (40.5)	340 (42.2)
Race			
White	367 (94.3)	388 (93.0)	755 (93.7)
Non-White	22 (5.7)	28 (6.7)[1]	50 (6.2)[1]
Region			
North America	26 (6.7)	25 (6.0)	51 (6.3)
South America	36 (9.3)	45 (10.8)	81 (10.0)
Western Europe	11 (2.8)	19 (4.6)	30 (3.7)
Eastern Europe	297 (76.3)	308 (73.9)	605 (75.1)
Rest of World	19 (4.9)	20 (4.8)	39 (4.8)
Prior Antibiotic Use			
Yes	224 (57.6)	239 (57.3)	463 (57.4)
No	165 (42.4)	178 (42.7)	343 (42.6)
Renal function, CrCl			
< 50 mL/min	23 (5.9)	13 (3.1)	36 (4.5)
≥ 50 to 80 mL/min	98 (25.2)	109 (26.1)	207 (25.7)
≥ 80 mL/min	268 (68.9)	295 (70.7)	563 (69.9)
Infection Type			
Bowel	77 (19.8)	80 (19.2)	157 (19.5)
Other	312 (80.2)	337 (80.8)	649 (80.5)
APACHE II Score[1]			
< 10	310 (79.7)	347 (83.2)	657 (81.5)
≥ 10	78 (20.1)	70 (16.8)	148 (18.4)

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Number of Abscesses Present			
≥ 1	219 (56.3)	240 (57.6)	459 (56.9)
= 1 (Single)	186 (47.8)	208 (49.9)	394 (48.9)
> 1 (Multiple)	33 (8.5)	32 (7.7)	65 (8.1)
0 (No abscess)	170 (43.7)	177 (42.4)	347 (43.1)
Peritonitis Present			
Yes	337 (86.6)	340 (81.5)	677 (84.0)
Local peritonitis	198 (50.9)	203 (48.7)	401 (59.2)
Diffuse peritonitis	139 (35.7)	137 (32.9)	276 (40.8)
No peritonitis	52 (13.4)	77 (18.5)	129 (16.0)
Anatomic Site of Infection			
Appendix	175 (45.0)	203 (48.7)	378 (46.9)
Non-Appendix	214 (55.0)	214 (51.3)	428 (53.1)
Failure of Prior Therapy			
Yes	24 (6.2)	21(5.0)	45 (5.6)
No	365 (93.8)	396 (95.0)	761 (94.4)
Bacteremia			
Yes	8 (2.1)	12 (2.9)	20 (2.5)
No	381 (97.9)	405 (97.1)	786 (97.5)
Procedure Type			
Percutaneous Aspiration	24 (6.2)	37 (8.9)	61 (7.6)
Laparoscopy	86 (22.1)	105 (25.2)	191 (23.7)
Laparotomy	274 (70.4)	271 (65.0)	545 (67.6)
Other	5 (1.3)	4 (1.0)	9 (1.1)

[1] One patient in the ceftolozane/tazobactam + metronidazole arm did not have an APACHE II Score assessed at baseline.

Source: Reviewer Table

Reviewer Comments: *Further details regarding the number of patients with prior antibiotic use by duration (< 24 hours vs. ≥ 24 hours), dosage (single dose vs. multiple doses) and timing relative to the initial abdominal procedure (before procedure vs. after procedure) is shown in the Appendix,* ***Tables 28 & 29****.*

3.2.3 Statistical Methodologies

Statistical Methodologies (Applicant)

The primary efficacy analysis was performed in the MITT population. The NI test was a 1-sided hypothesis test performed at the 2.5% level of significance and was based on the lower limit of the 2-sided 95% confidence interval (CI). The primary efficacy outcome measure was the clinical cure rate at 24 to 32 days after first dose of study drug. The primary efficacy analysis was adjusted for the randomization stratification factor of disease type (bowel, other site) and region (Eastern Europe, North America, Rest of World, South America, Western Europe).

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The number and percentage of patients in each treatment group defined as a clinical cure and clinical failure/indeterminate were tabulated. The null and alternative hypotheses were as follows where p_1 was the rate of the primary efficacy outcome measure in the ceftolozane/tazobactam + metronidazole treatment group, p_2 was the rate of the primary efficacy outcome measure in meropenem treatment group, and Δ was the NI margin of 10%:

$$H_0 : p_1 - p_2 \leq -\Delta$$
$$H_1 : p_1 - p_2 > -\Delta$$

To test the null hypothesis, a 2-sided 95% CI for the observed difference in primary outcome rates (ceftolozane/tazobactam + metronidazole minus meropenem) was calculated. If the lower limit of the 95% CI for the treatment difference in the ITT population exceeded –10%, then the null hypothesis was rejected and the non-inferiority of ceftolozane/tazobactam to meropenem was concluded. The 2-sided 95% CI for non-inferiority testing based on the difference of clinical cure rates at the TOC visit was computed using the stratified Newcombe CI with Minimum Risk weights[2] as described by Yan and Su[3]. As a supportive analysis, unstratified analyses, with a 2-sided 95% Wilson Score CI for individual proportions and proportion differences (treatment – control), were also provided.

The statistical approach above was also used in the secondary efficacy analysis which tested the noninferiority of ceftolozane/tazobactam plus metronidazole versus meropenem with respect to the proportion of subjects who achieved clinical cure at the TOC visit in the ME population.

NI Margin (Delta) Selection: A 10% non-inferiority margin was used to determine treatment efficacy in the primary analysis. A 10% NI margin was agreed to by the Agency prior to the submission and can be supported by risk differences in event rates (death or intra-abdominal or surgical infection) between recipients of antibacterial drug prophylaxis and recipients of placebo/no treatment in historical trials of antibacterial drug prophylaxis.

Interim Analyses: There were no interim analyses conducted.

Missing Data: Missing data were primarily handled with a data as observed (DAO) approach for the ME, Expanded ME, and CE populations and a treatment failure approach for the MITT population, which is defined as follows: For the analysis of clinical response at the TOC visit in the MITT population, subjects with a missing clinical response, including indeterminate, were categorized as treatment failures.

Multiple Comparisons Adjustment: In the Applicant's primary hypotheses, only one statistical hypothesis was tested. Provided the primary hypothesis was rejected, only one secondary hypothesis was tested. Therefore, no adjustments were made to control for inflation of the type I error rate in either the primary and secondary analyses.

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Covariates: No adjustments for covariates were made to the primary analyses.

Statistical Methodologies (Reviewer)

Similar to the Applicant's primary analysis, the Reviewer's primary analyses evaluated non-inferiority within a 10% margin based on the lower 95% confidence limit of the treatment difference in clinical cure rates at TOC (ceftolozane/tazobactam + metronidazole minus meropenem) being at least -10%. However, due to concerns with the Applicant's approach of computing confidence limits using a stratified Newcombe CI with Minimum Risk weights (e.g. small numbers of subjects in some of the strata and unstable stratum weights where one stratum weight was less than 0), the Reviewer's analyses considered unstratified primary analyses, with a 2-sided 95% Wilson Score CI for proportion differences (treatment – control). This approach was the Applicant's pre-specified primary analysis approach, conditional upon assumptions of the stratified analysis not being met.

Similar to the Applicant's primary analysis, patients with missing or indeterminate data at the TOC visit were considered as failures.

As discussed in **Sections 4 & 5**, the Reviewer also conducted sensitivity, exploratory and subgroup analyses using the same methodology as described above. These analyses included:

- Sensitivity analyses in other analysis populations and different timings of assessment
- Sensitivity analysis with re-classifications of primary outcome (e.g. SRP, additional surgeries, concomitant medications,).
- Exploratory analyses by protocol
- Subgroup analyses by age, gender, race, geographic region
- Subgroup analyses by other baseline prognostic factors

Reviewer Comments: *Unless otherwise stated, the Reviewer's analyses consider the MITT population and compute 95% confidence intervals as Wilson Score CIs (unadjusted).*

3.2.4 Results and Conclusions

Primary and Secondary Analyses

The results of the primary analysis are shown in **Table 6**. Based on the Reviewer's analysis, clinical cure rates were lower in the ceftolozane/tazobactam + metronidazole arm than in the comparator (meropenem) arm at 83.0% vs. 87.3%, a treatment difference of -4.3% (95% CI: -9.2, 0.7). Since the lower limit of the treatment difference was slightly above the minimum requirement for non-inferiority, the primary analysis finding was considered to be supportive of non-inferiority. The primary analysis was negatively impacted by a larger percentage of ceftolozane/tazobactam + metronidazole patients with indeterminate outcomes 34/389 (8.7%) vs. 19/417 (4.6%) counted as failure outcomes.

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In **Table 6**, a secondary analysis compared clinical cure rates at TOC in the ME population. Clinical cure rates for ceftolozane/tazobactam + metronidazole vs. meropenem were 94.2% vs. 94.7%, a difference of -0.5% (95% CI: -4.5, 3.2) which was supportive of non-inferiority.

Reviewer Comments: The *MITT analysis population was considered to be more informative than the ME population for treatment comparisons in clinical cure rates. Analyses in the ME population, such as the Applicant's secondary analysis, are limited by the post-baseline exclusion of patients which can lead to potential biases, especially if the post-baseline exclusions are dependent upon the effect of the study drug.*

Table 6: Primary and Secondary Analysis, Clinical Response at TOC (MITT & ME)

	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)	
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: Reviewer Table

Reviewer Comments: *The Applicant's primary analysis was based on a 95% stratified Newcombe CI with Minimum Risk weights using primary site of infection and region as stratification factors. However, due to concerns with the reliability of this approach given the small numbers of subjects in some of the strata and unstable stratum weights (e.g. one stratum weight was less than 0), the Reviewer considered an unstratified approach in the primary analysis. An unstratified approach was the Applicant's pre-specified primary analysis approach, conditional upon assumptions of the stratified analysis not being met. Other approaches designed to better address possible differences related to the protocol, such as the use of a stratified Newcombe CI [3] or a random effects model (Dersimonian and Laird [4]), provided results which were similar or slightly less conservative than results from an unstratified approach. These approaches showed treatment differences of -4.1% (95% CI: -9.1%, 0.8%) and -4.1% (95%*

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CI: -8.9%, 0.8%) respectively vs. -4.3% (95% CI: -9.2%, 0.7%) using an unstratified approach, ***Table 17*** and ***Figure 3.***

Table 7 shows the number of subjects assessed as a clinical failure in the primary analysis and the reasons for those failures. The percentage of failures was similar in each of the treatment arms at 8.2%. Comparing reasons for failure between the treatment arms, a larger percentage of ceftolozane/tazobactam + metronidazole failures were due to 'treatment with additional antibiotics for ongoing symptoms of IAI' and 'post-surgical wound infection' and a slightly lower percentage was due to a 'persisting or recurrent infection within the abdomen requiring additional intervention to cure the infection.'

Table 7: Reasons for Clinical Response of Failure in Primary Analysis (MITT Population)

	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	**Meropenem (N=417)** n (%)	**Total (N=806)** n (%)
Subjects with Clinical Response of Failure	**32 (8.2)**	**34 (8.2)**	**66 (8.2)**
Reason for Failure:			
Death Related to IAI	0 (0.0)	1 (0.2)	1 (0.1)
Persisting or recurrent infection within the abdomen requiring additional intervention to cure infection	11 (2.8)	15 (3.6)	26 (3.2)
Treatment with additional antibiotics for ongoing symptoms of IAI	13 (3.3)	11 (2.6)	24 (3.0)
Post-surgical wound infection	8 (2.1)	7 (1.7)	15 (1.9)

Source: Reviewer Table

Table 8 shows the reasons for indeterminate clinical responses in the primary analysis which were more prevalent in the ceftolozane/tazobactam + metronidazole than in the meropenem arm at 34 (8.7%) vs. 19 (4.6%). This imbalance was driven primarily by 21 (5.4%) of subjects in the ceftolozane/tazobactam + metronidazole arm compared to 11 (2.6%) of subjects in the meropenem arm prematurely discontinuing study drug, including those discontinuing due to AEs, 10 (2.6%) vs. 4 (1.0%). There were also more subjects in the ceftolozane/tazobactam + metronidazole arm with a clinical response of cure at EOT & LFU who had no TOC assessment, 5 (1.3%) vs. 1 (0.2%).

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Table 8: Reasons for Indeterminate Clinical Response in Primary Analysis (MITT)

	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Total (N=806) n (%)
Subjects with a Clinical Response of Indeterminate at TOC	**34 (8.7)**	**19 (4.6)**	**53 (6.6)**
Clinical Response of Cure at EOT & LFU visit but no TOC assessment	5 (1.3)	1 (0.2)	6 (0.7)
Cure at EOT but Discontinued Study	5 (1.3)	5 (1.2)	10 (1.2)
Adverse Event	1 (0.3)	3 (0.7)	4 (0.5)
Withdrawal by Subject	1 (0.3)	1 (0.2)	2 (0.2)
Lost to Follow-up	3 (0.8)	1 (0.2)	4 (0.5)
Number of Subjects Prematurely Discontinuing Study Drug	21 (5.4)	11 (2.6)	32 (4.0)
Adverse Event	10 (2.6)	4 (1.0)	14 (1.7)
Protocol Violation	1 (0.3)	0 (0.0)	1 (0.1)
Withdrawal by Subject	9 (2.3)	5 (1.2)	14 (1.7)
Other	1 (0.3)	2 (0.5)	3 (0.4)
Death not related to IAI prior to TOC	7 (1.8)	5 (1.2)	12 (1.5)
Randomized Not Treated	1 (0.3)	3 (0.7)	4 (0.5)

Patients may be included in more than one major category.
Source: Reviewer Table

Reviewer Comments*: These missing/indeterminate outcomes were not assumed to be occurring at random since the underlying mechanism for this occurrence and the associated role of the study drug is not clear. Consequently, sensitivity analyses relying on the assumption of missing/indeterminate outcomes occurring at random (e.g. multiple imputation) were not performed. Note that the Applicant's primary analysis pre-specified an approach which counted all patients with missing/indeterminate outcomes as failures. Such an approach is generally conservative when the percentage of patients with missing/indeterminate outcomes is larger in the treatment arm than in the comparator arm, as was observed in Trial -08&09.*

Table 9 shows clinical cure rates in patients at TOC by baseline pathogen in the MITT population. Cure rates were numerically lower in ceftolozane/tazobactam + metronidazole vs. meropenem patients for most pathogens, namely aerobic gram-positive pathogens, 79.3% vs. 87.8% and anaerobic gram-negative pathogens, 81.8% vs. 91.6%.

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Table 9: Clinical Cure Rates at TOC by Baseline Pathogen (MITT)

Organism Group **Pathogen**	**Ceftolozane/ Tazobactam + Metronidazole (N=389)** n/N (%)	**Meropenem (N=417)** n/N (%)
Aerobic Gram-negative	263/313 (84.0)	303/346 (87.6)
Escherichia coli	216/255 (84.7)	238/270 (88.2)
Klebsiella pneumonia	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)

Source: Reviewer Table

Conclusions

Efficacy findings in the Reviewer's primary analysis of clinical cure rates at TOC in the MITT population demonstrated non-inferiority based on the treatment difference of -4.3% (95% CI: -9.2%, 0.7%) where the lower confidence limit of -9.2% fell slightly above the required NI limit of -10%. Primary analysis findings were negatively impacted by a larger percentage of ceftolozane/tazobactam plus metronidazole patients vs. meropenem patients with missing/indeterminate assessments at TOC who were evaluated as failures.

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3.3 Evaluation of Safety

As shown in **Tables 10-13,** comparisons of adverse events/reactions observed in Trial-08&09 tended to be less favorable among those patients receiving ceftolozane/tazobactam. There were also more deaths reported in patients receiving ceftolozane/tazobactam. For further details regarding the evaluation of safety, refer to the clinical review conducted by Dr. Maria Allende.

In **Table 10,** rates for adverse reactions (except vomiting and dizziness) were higher in patients receiving ceftolozane/tazobactam. Rates for the most common adverse reactions of nausea and diarrhea were 7.9% vs. 5.8% and 6.2% vs. 5.0%, respectively.

Table 10: Adverse Reactions in Trial-08&09 (Safety Population)

Adverse Reactions[1]	**Ceftolozane/ Tazobactam+ Metronidazole (N=482)** n (%)	**Meropenem (N=497)** n (%)
Nausea	38 (7.9)	29 (5.8)
Headache	12 (2.5)	9 (1.8)
Diarrhea	30 (6.2)	25 (5.0)
Pyrexia	26 (5.2)	20 (4.0)
Constipation	9 (1.9)	6 (1.2)
Insomnia	17 (3.5)	11 (2.2)
Vomiting	16 (3.3)	20 (4.0)
Hypokalemia	14 (2.9)	8 (1.6)
ALT increased	7 (1.5)	5 (1.0)
AST increased	5 (1.0)	3 (0.6)
Anemia	6 (1.2)	4 (0.8)
Thrombocytosis	9 (1.9)	5 (1.0)
Abdominal pain	6 (1.2)	2 (0.4)
Anxiety	9 (1.9)	7 (1.4)
Dizziness	4 (0.8)	5 (1.0)
Hypotension	8 (1.7)	4 (0.8)
Atrial fibrillation	6 (1.2)	3 (0.6)
Rash	8 (1.6)	7 (1.4)

[1] Adverse reactions occurring in ≥ 1% of Patients Receiving ceftolozane/tazobactam
Source: Reviewer Table

Table 11 compares treatment emergent adverse events (TEAEs) between patients receiving ceftolozane/tazobactam (plus metronidazole) and patients receiving meropenem. A higher percentage of patients receiving ceftolozane/tazobactam had a TEAE, serious adverse event

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(SAE) or a TEAE leading to discontinuation of study drug or death. There was a slightly lower percentage of patients receiving ceftolozane/tazobactam, with a treatment related TEAE.

Table 11: Treatment Emergent Adverse Events in Trial-08&09 (Safety Population)

Adverse Reactions[1]	**Ceftolozane/Tazobactam + Metronidazole (N=482)** n (%)	**Meropenem (N=497)** n (%)
Any TEAE	212 (44.0)	212 (42.7)
Any SAE	39 (8.1)	36 (7.2)
Any TEAE Leading to Discontinuation of Study Drug	13 (2.7)	11 (2.2)
Any TEAE Resulting in Death	11 (2.3)	8 (1.6)
Any Treatment Related TEAE	39 (8.1)	44 (8.9)
Any Treatment Related SAE	1 (0.2)	1 (0.2)
Any Treatment Related TEAE Leading to Discontinuation of Study Drug	3 (0.6)	4 (0.8)
Any Treatment Related TEAE Resulting in Death	0	0

[1] Adverse reactions occurring in ≥ 1% of Patients Receiving ceftolozane/tazobactam
Source: Partially adapted from Table 13 of Summary of Clinical Safety

Table 12 shows that there were more deaths observed in patients receiving ceftolozane/tazobactam + metronidazole vs. meropenem in both the Phase 2 and Phase 3 trials (Trials -01 and -08&09). Trial -08&09 showed mortality rates of 11/482 (2.3%) vs. 8/497 (1.6%) while Trial -01 showed rates of 3/82 (3.7%) vs. 0/39 (0%). Combining these 2 trials, mortality rates were 14/564 (2.5%) vs. 8/536 (1.5%). Adjusting for the difference in size of the trials, the weighted treatment difference was 1.0% (95% CI: -0.9%, 2.8%).

Table 12: All-cause Mortality Rates in CIAI Studies

All-cause Mortality Rate	**Ceftolozane/ Tazobactam+ Metronidazole** n (%)	**Meropenem** n (%)	**Adjusted Difference (95% CI)**
Trial -01	3/82 (3.7)	0/39 (0.0)	
Trial -08&09	11/482 (2.3)	8/497 (1.6)	
Combined Trials	14/564 (2.5)	8/536 (1.5)	1.0% (-0.9%, 2.8%)[1]

[1]The difference was adjusted by trial using a stratified Newcombe 95% CI with Minimum Risk Weights.
Source: Reviewer Table

Table 13 provides a listing of the subjects in the cIAI studies with a death and the cause of death (as stated in **Table 12**). Overall there did not appear to be a clear trend related to differences in the age/sex of the patients or the cause of death. However, there were more patients in the ceftolozane/tazobactam + metronidazole arm listed as having a cause of death due to multi-organ

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failure, renal failure or sudden death. It should be noted that none of deaths described in **Table 13** were considered by the Applicant to be related to the study drug.

Table 13: Individual Deaths in CIAI Studies

Ceftolozane/Tazobactam + Metronidazole (N=14)			Meropenem (N=8)[1]		
Subject	**Age/Sex**	**Cause of Death[2]**	**Subject**	**Age/Sex**	**Cause of Death**
Phase 2 Trial -01					
7107-IA023	83/F	Urologic sepsis			
7302-IA052	43/F	Pulmonary embolism			
9312-IA117	48/M	Renal failure, cardio-respiratory arrest			
Phase 3 Trial -08&09					
1008-4020-013	81/F	Lung Infection pseudomonal	1008-4129-008	63/F	Circulatory collapse
1008-4127-002	66/M	Cardiac failure	1008-4720-001	58/M	Septic shock
1008-4127-025	73/M	Multi-organ failure	1009-6477-006	69/M	Atrial fibrillation, Graft infection
1009-4206-003	55/F	Renal failure acute	1008-6652-015	58/M	Road traffic accident
1008-4714-008	81/M	Ischemic stroke, Multi-organ failure	1008-7404-006	80/F	Septic shock
1009-4811-003	74/F	Myocardial infarction	1008-8106-004	41/M	Cardiovascular insufficiency
1009-5412-001	59/F	Sudden death	1009-6477-008	81/F	Myocardial infarction
1009-6275-019	79/M	Sudden death	1008-8108-001	88/F	Pulmonary embolism
1009-6276-006	60/M	Multi-organ failure, Septic shock			
1009-6376-009	76/F	Cardiogenic shock			
1009-9003-001	80/F	Cardiopulmonary failure			

[1] There were no deaths in the meropenem arm in Trial-01
[2] None of the 22 deaths described were considered by the Applicant to be related to the study drug
Source: Reviewer Table

4. SENSITIVITY/EXPLORATORY ANALYSES

4.1 Sensitivity Analyses

Various sensitivity analyses were performed to investigate the robustness of findings in the primary analysis. These analyses considered treatment differences in other analysis sets (e.g. MITT patients receiving study therapy, patients without violations of inclusion/exclusion criteria), the timing of clinical response (e.g. EOT or LFU), various adjustment (stratification) factors (e.g. region, infection type, protocol) and re-classifications of the primary outcome (e.g. SRP re-

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classifications, additional surgeries or use of concomitant medications). As shown below, these analyses were consistently less favorable in the ceftolozane/tazobactam + metronidazole arm but were still supportive of non-inferiority (i.e. the lower 95% confidence limit for the treatment difference was ≥ -10%). Note that these post-hoc analyses may be limited by inflation of the overall type I error rate from multiple testing as well as treatment imbalances resulting from the exclusion of some patients in the analysis.

MITT Subjects Receiving Study Therapy

As shown in **Table 14**, an analysis was performed including only those MITT patients who received study therapy. Compared to the primary analysis, this analysis removed 4 subjects who had been counted as failures (1 patient in the ceftolozane/tazobactam + metronidazole arm and 3 patients in the meropenem arm). This resulted in comparisons which were less favorable to the ceftolozane/tazobactam + metronidazole arm. Clinical cure rates were 83.3% vs. 87.9%, a difference of -4.7% (-9.6, 0.2) which was still supportive of non-inferiority.

Table 14: Clinical Cure Rates at TOC in MITT Patients Receiving Treatment

Clinical Response	Ceftolozane/ Tazobactam + Metronidazole (N=388) n (%)	Meropenem (N=414) n (%)	Difference (95% CI)
Cure	323 (83.3)	364 (87.9)	-4.7 (-9.6, 0.2)
Failure	32 (8.2)	34 (8.2)	
Indeterminate	33 (8.5)	16 (3.9)	

Source: Reviewer Table

MITT (Removing Patients with Entry Criteria Violations)

In **Table 15** and **Figure 2**, the Reviewer's sensitivity analyses also considered primary analysis results in the MITT population after removing patients with any entry criteria violations (i.e. 49 MITT patients). Although comparisons were still less favorable in ceftolozane/tazobactam + metronidazole arm at 309/366 (84.4%) vs. 343/391 (87.7%), the treatment difference of -3.3% (95% CI: -8.3%, 1.6%) was less pronounced than in the primary analysis. Treatment differences were also less pronounced after removing individual entry criteria (listed below) with a lower confidence limit ranging from -8.3% to -8.9% vs. -9.2% in the primary analysis.

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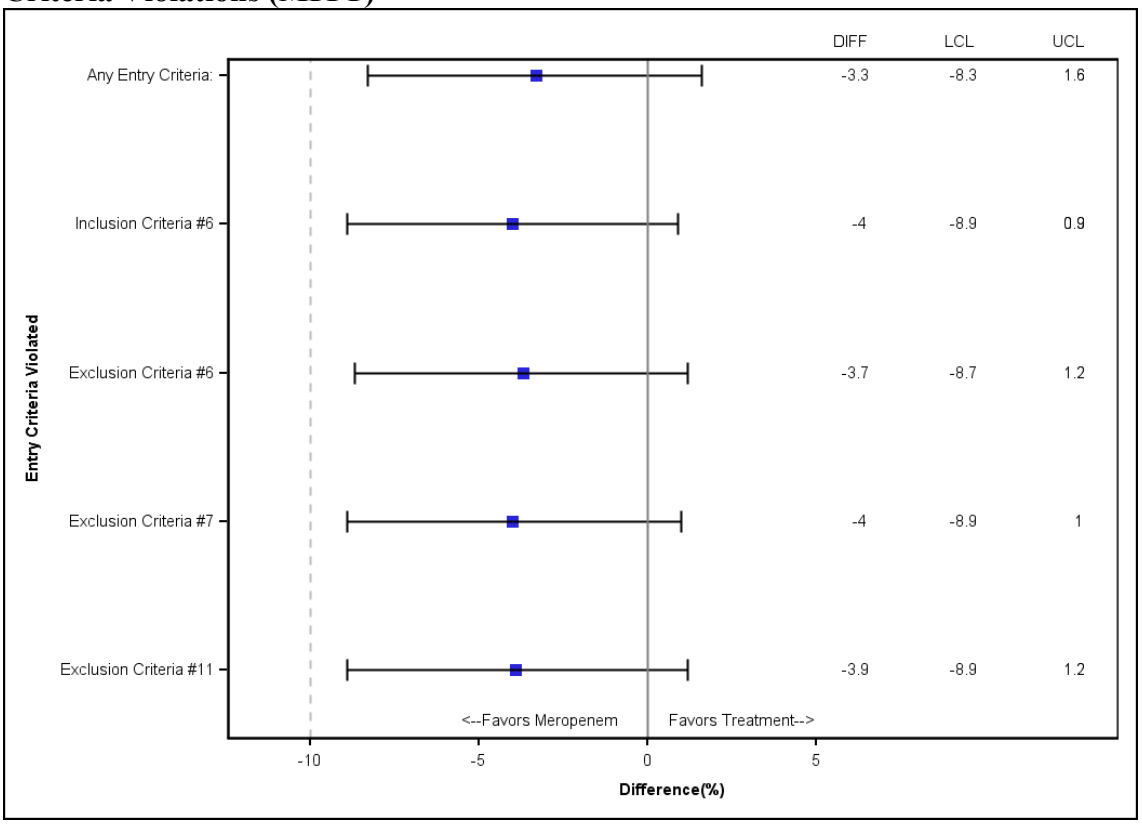
Table 15: Clinical Response Removing Patients with Entry Criteria Violations (MITT)

Entry Criteria Used[1]:	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Difference (95% CI)
Any entry criteria	**309/366 (84.4)**	**343/391 (87.7)**	**-3.3% (-8.3, 1.6)**
Inclusion Criteria #6- Surgical intervention within 24 hrs of (before or after) first dose of study drug.	323/388 (83.3)	362/415 (87.2)	-4.0% (-8.9, 0.9)
Exclusion Criteria #6- Use of systemic abx for > 24 hrs prior to first dose of study drug, if not prior failure.	315/376 (83.8)	357/408 (87.5)	-3.7% (-8.7, 1.2)
Exclusion Criteria #7- > 1 dose of non-study abx given post-op. If enrolled pre-op, no post-op abx was allowed.	320/383 (83.6)	357/408 (87.5)	-4.0% (-8.9, 1.0)
Exclusion Criteria #11- Hepatic disease at baseline	321/385 (83.4)	357/409 (87.3)	-3.9% (-8.9, 1.2)

[1] Patients may have multiple entry criteria violations

Source: Reviewer Table

Figure 2: Treatment Differences in Clinical Response Removing Patients with Entry Criteria Violations (MITT)



Source: Reviewer Figure

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Timing on Clinical Response

To investigate the effect of timing on clinical responses, sensitivity analyses considered clinical cure rates in the MITT population at visits other than the TOC visit, including the EOT and LFU visits. As shown in **Table 16**, treatment differences observed at the EOT and LFU visits were less favorable in the ceftolozane/tazobactam + metronidazole arm as compared to the meropenem arm. However, the lower bound of the 95% confidence interval for the treatment difference was greater than -10% (i.e. -7.2% at EOT and -9.1% at LFU) which supported non-inferiority.

Table 16: Clinical Response at EOT and LFU (MITT Population)

Clinical Response	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Difference (95% CI)
EOT Visit			
Cure	347 (89.2)	385 (92.3)	-3.1% (-7.2, 0.9)
Failure	17 (4.4)	18 (4.3)	
Indeterminate	25 (6.4)	14 (3.4)	
LFU Visit			
Sustained Clinical Cure	321 (82.5)	361 (86.6)	-4.1% (-9.1, 0.9)
Failure	32 (8.2)	34 (8.2)	
Relapse	0 (0.0)	2 (0.5)	
Indeterminate	36 (9.3)	20 (4.8)	

Source: Reviewer Table

Adjustment (Stratification) Factors

To investigate the effect of the adjustment factors on clinical responses, sensitivity analyses considered clinical cure rates in the MITT population using various assumptions for stratification, **Table 17** and **Figure 3**. Compared to the Reviewer's primary unadjusted analysis which found a treatment difference of -4.3% (95% CI: -9.2, 0.7), the adjusted analyses showed lower confidence limits ranging from -8.9% to -9.4% which were also supportive of non-inferiority. The upper confidence limits fell within a range of 0.1% to 0.8% which was only slightly above 0, a level generally indicative of statistical inferiority (i.e. upper limit less than 0).

Table 17: Clinical Cure Rates at TOC by Adjustment (Stratification) Factors (MITT)

Adjustment (Stratification) Factor:	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Difference (95% CI)
Unadjusted (unstratified)	323 (83.0)	364 (87.3)	-4.3% (-9.2, 0.7)[1]
eCRF Site of Infection and Region	323 (83.0)	364 (87.3)	-4.2% (-8.9, 0.5)[2,3]

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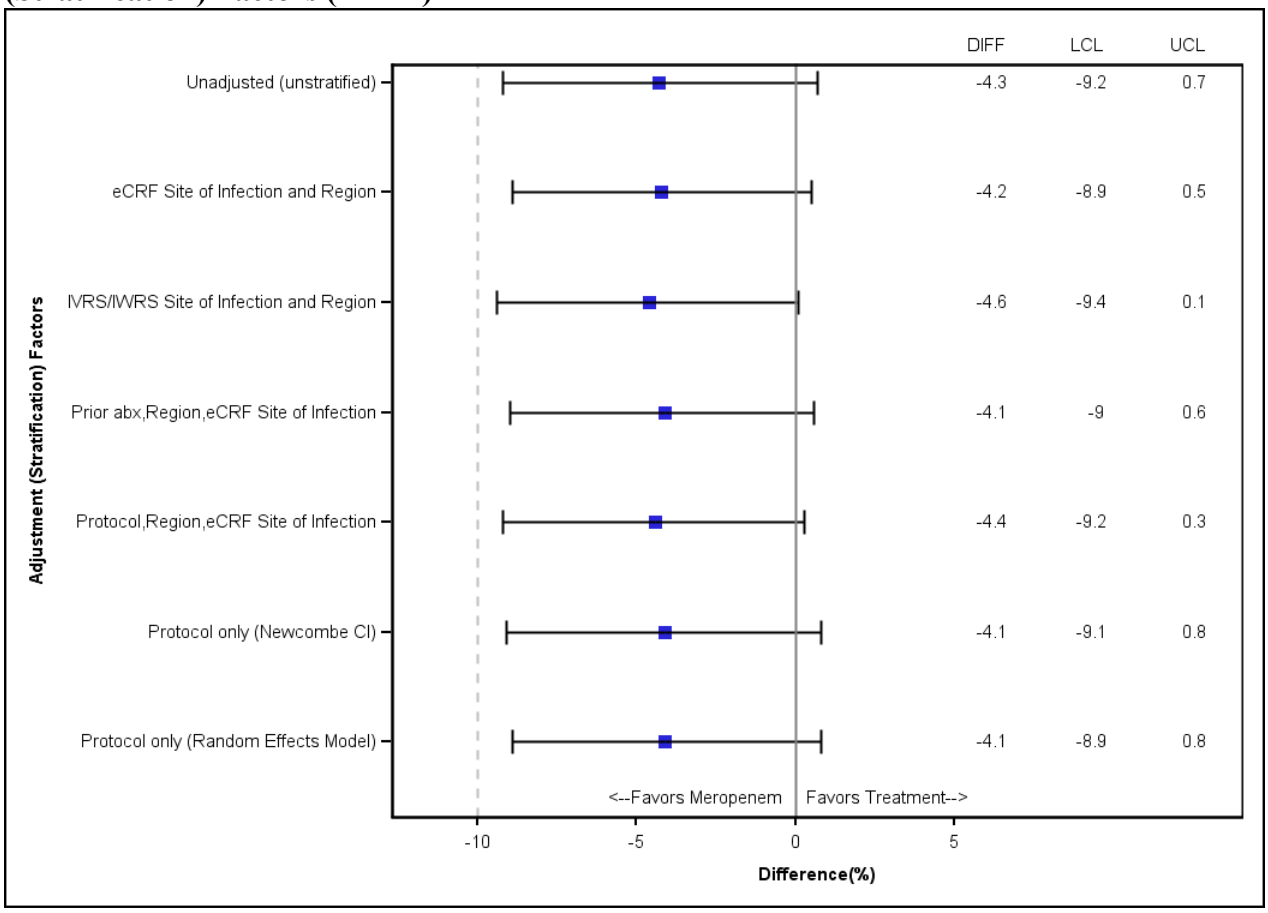
IVRS/IWRS Site of Infection and Region	323 (83.0)	364 (87.3)	-4.6% (-9.4, 0.1)[2]
Prior abx[4], Region & eCRF Site of Infection	323 (83.0)	364 (87.3)	-4.1% (-9.0, 0.6)[2]
Protocol, Region & eCRF Site of Infection	323 (83.0)	364 (87.3)	-4.4% (-9.2, 0.3)[2]
Protocol Only (Newcombe CI)	323 (83.0)	364 (87.3)	-4.1% (-9.1, 0.8)[2]
Protocol Only (Random Effects Model)	323 (83.0)	364 (87.3)	-4.1% (-8.9, 0.8)[5]

[1] Reviewer Primary Analysis using 95% Wilson Score CIs
[2] 95% Newcombe CI with Minimum Risk weights
[3] Applicant's pre-specified primary analysis
[4] Refers to any prior antibiotic therapy taken within 24 hrs before the first dose of the treatment
[5] Random Effects Model using Dersimonian and Laird Method
Source: Reviewer Table

Figure 3: Treatment Differences in Clinical Cure Rates at TOC Using Various Adjustment (Stratification) Factors (MITT)



Source: Reviewer Figure

Reviewer Comments: *As noted previously, the adjusted analyses above with region and site of infection as factors may not be reliable due to small numbers of subjects in some of the strata and*

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unstable stratum weights. For these reasons, these approaches were not considered in the primary analyses but were included as sensitivity analyses.

Re-classification of Primary Outcome

In **Tables 18-20**, sensitivity analyses also evaluated findings for the primary outcome at TOC in which patients were re-classified from a 'clinical cure' to an 'indeterminate/failure' for various reasons such as an indeterminate/failure assessment by the surgical review panel (SRP), a second/third procedure performed after 72 hours from the initial procedure and use of concomitant antibiotics (any use or use to treat a distal infection). Although these sensitivity analyses showed less favorable treatment differences in the ceftolozane/tazobactam + metronidazole arm across a broad range of conditions, differences were similar or less pronounced than in the primary analysis and still narrowly supportive of non-inferiority.

Table 18: Clinical Response Including SRP Reclassification (MITT)

Clinical Response at TOC	**Ceftolozane/ Tazobactam + Metronidazole (N=389)** n (%)	**Meropenem (N=417)** n (%)	**Difference (95% CI)**
Cure	321 (82.5)	360 (86.3)	-3.8% (-8.9, 1.2)
Failure	22 (5.7)	26 (6.2)	
Indeterminate	46 (11.8)	31 (7.4)	

Source: Reviewer Table

Table 19: Clinical Response by Second/Third Abdominal Procedure Occurring More Than 72 hours After Enrollment (MITT)

Clinical Response at TOC	**Ceftolozane/ Tazobactam + Metronidazole (N=389)** n (%)	**Meropenem (N=417)** n (%)	**Difference (95% CI)**
Clinical Cure	317 (81.5)	351 (84.2)	-2.7% (-7.9, 2.5)
Failure	72 (18.5)	66 (15.8)	

Source: Reviewer Table

Table 20: Clinical Response by Concomitant Antibiotic Use (MITT)

Clinical Response at TOC	**Ceftolozane/ Tazobactam + Metronidazole (N=389)** n (%)	**Meropenem (N=417)** n (%)	**Difference (95% CI)**
'Cures' using any concomitant antibiotics reclassified as failures			
Clinical Cure	305 (78.4)	344 (82.5)	-4.1% (-9.6, 1.4)

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Failure	84 (21.6)	73 (17.5)	
'Cures' using a concomitant antibiotics to treat distal infection reclassified as failures			
Clinical Cure	318 (81.8)	355 (85.1)	-3.4% (-8.6, 1.8)
Failure	71 (18.3)	62 (14.9)	

Source: Reviewer Table

4.2. Exploratory Analyses

Comparisons of Prognostic Factors in Protocols -08 and -09

As discussed previously, data from two identical cIAI trials following separate protocols (Protocol -08 and Protocol -09) were pooled to support a single, adequately powered Phase 3 study, Study -08&09. During the design stage of Trial -08&09, the Division considered pooling to be acceptable due to the similarity of Protocols -08 and -09. These protocols had identical entry criteria, primary efficacy variables, trial drug dosing regimen, comparator, treatment duration, outcome and safety assessments.

In **Table 21,** the Reviewer's exploratory analyses compared prognostic factors for Protocols -08 vs. -09. **Figure 4** further compares Protocols -08 vs. -09 by 11 risk factors identified by the Reviewer as being potentially associated with lower cure rates. These factors included: age ≥ 65 years, race of 'non-white', region of 'N.America/W.Europe/ROW', use of prior antibiotics, primary site of infection in the bowel, anatomic site of infection of non-appendix, CrCl > 50ml/min, APACHE II Score ≥ 10, multiple abscesses, no peritonitis and a procedure of percutaneous aspiration. While comparisons failed to show strong heterogeneity across protocols that would prohibit pooling, they did show differences between protocols for 3 risk factors including use of prior antibiotics (47.2% vs. 68.1%), region of N.America/W.Europe/Rest of World (17.5% vs. 12.2%) and age ≥ 65 (19.5% vs. 26.6%). Since such differences can potentially result in imbalances and confounding in the primary analysis, the Reviewer conducted further sensitivity analyses. These analyses showed that adjusting for the protocol had a minimal effect on primary analysis findings, **Table 17**.

Table 21: Number (%) of Patients with Prognostic Factors at Baseline by Protocol (MITT)

	-08 Protocol (N=411) n (%)	**-09 Protocol (N=395)** n (%)	**Total (N=806)** n (%)
Age (Years)			
Mean (Std. dev.)	49.5 (17.5)	51.7 (17.5)	50.6 (17.5)
Median (Min, Max)	51 (18, 92)	53 (18, 92)	52 (18, 92)
Age Group			
≥ 18 to < 65	331 (80.5)	290 (73.4)	621 (77.0)
≥ 65	80 (19.5)	105 (26.6)	185 (23.0)
≥ 75	36 (8.8)	47 (11.9)	83 (10.3)
Gender			

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Male	237 (57.7)	229 (58.0)	466 (57.8)
Female	174 (42.3)	166 (42.0)	340 (42.2)
Race			
White	390 (94.9)	365 (92.4)	755 (93.7)
Non-white	21 (5.1)	29 (7.4)[1]	50 (6.2)[1]
Region			
North America	40 (9.7)	11 (2.8)	51 (6.3)
South America	26 (6.3)	55 (13.9)	81 (10.0)
Western Europe	27 (6.6)	3 (0.7)	30 (3.7)
Eastern Europe	313 (76.2)	292 (73.9)	605 (75.1)
Rest of World	5 (1.2)	34 (8.6)	39 (4.8)
Prior Antibiotics Use			
Yes	194 (47.2)	269 (68.1)	463 (57.4)
No	217 (52.8)	126 (31.9)	343 (42.6)
Renal function, CrCl			
< 50 mL/min	17 (4.1)	19 (4.8)	36 (4.5)
≥ 50 to 80 mL/min	101 (24.6)	106 (26.8)	207 (25.7)
≥ 80 mL/min	293 (71.3)	270 (68.4)	563 (69.9)
Infection Type			
Bowel	83 (20.2)	74 (18.7)	157 (19.5)
Other	328 (79.8)	321 (81.3)	649 (80.5)
Baseline APACHE II Score			
< 10	330 (80.3)	327 (82.8)	657 (81.5)
≥ 10	81 (19.7)	67 (17.0)	148 (18.4)
Number of Abscesses Present			
≥ 1	239 (58.2)	220 (55.7)	459 (56.9)
= 1 (Single)	202 (49.1)	192 (48.6)	394 (48.9)
> 1 (Multiple)	37 (9.0)	28 (7.1)	65 (8.1)
0 (No abscess)	172 (41.8)	175 (44.3)	347 (43.1)
Peritonitis Present			
Yes	354 (86.1)	323 (81.8)	677 (84.0)
Local peritonitis	200 (48.7)	201 (50.9)	401 (49.8)
Diffuse peritonitis	154 (37.5)	122 (30.9)	276 (34.2)
No	57 (13.9)	72 (18.2)	129 (16.0)
Anatomic Site: Appendix			
Yes	197 (47.9)	187 (47.3)	384 (47.6)
No	214 (52.1)	208 (52.7)	422 (52.4)

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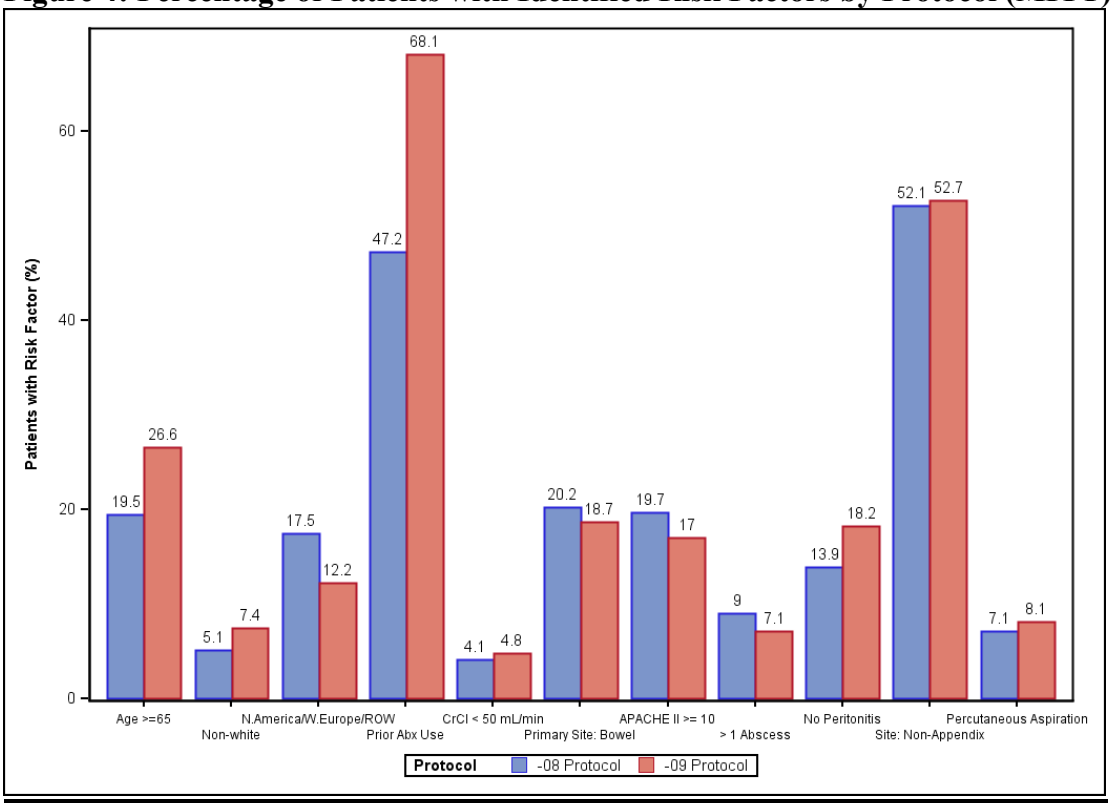
Failure of Prior Therapy			
Yes	24 (5.8)	21 (5.3)	45 (5.6)
No	387 (94.2)	374 (94.7)	761 (94.4)
Bacteremia			
Yes	11 (2.7)	9 (2.3)	20 (2.5)
No	400 (97.3)	386 (97.7)	786 (97.5)
Procedure Type			
Percutaneous Aspiration	29 (7.1)	32 (8.1)	61 (7.6)
Laparoscopy	101 (24.6)	90 (22.8)	191 (23.7)
Laparotomy	275 (66.9)	270 (68.4)	545 (67.6)
Other	6 (1.5)	3 (0.8)	9 (1.1)

[1] One patient in the Protocol -09 had a missing APACHE II Score

Source: Reviewer Table

Figure 4: Percentage of Patients with Identified Risk Factors by Protocol (MITT)



Source: Reviewer Figure

Comparisons of Primary Outcome in Protocols -08 and -09

Comparisons of the primary outcome in subjects originating from Protocol -08 vs. 09 were also performed, as shown in **Table 22**. In both treatment arms, subjects from Protocol -09 showed lower clinical cure rates than subjects from Protocol-08. In the ceftolozane/tazobactam + metronidazole arm, clinical cure rates were 80.1% in Protocol -09 vs. 85.9% in Protocol -08. Treatment differences (ceftolozane/tazobactam + metronidazole minus meropenem) were also less favorable in the treatment arm for Protocol -09 than for Protocol -08 at -6.2% (-13.6%, 1.2%) vs. -2.4% (-9.0, 4.1). These imbalances across protocols appear to have been influenced by more indeterminates in the ceftolozane/tazobactam + metronidazole arm for Protocol -09 vs. Protocol -08 at 11.0% vs. 6.6%. Although there were differences between protocols in the primary outcome as well as some risk factors (as previously shown), sensitivity analyses showed that the protocol variable had a minimal effect on primary analysis findings, **Table 17**.

Table 22: Clinical Cure Rates at TOC by Protocol (MITT)

Protocol	Clinical Response	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Difference (95% CI)
Protocol -08		N=198	N=213	
	Cure	170 (85.9)	188 (88.3)	-2.4 (-9.0, 4.1)
	Failure	15 (7.6)	16 (7.5)	
	Indeterminate	13 (6.6)	9 (4.2)	
Protocol -09		N=191	N=204	
	Cure	153 (80.1)	176 (86.3)	-6.2 (-13.6, 1.2)
	Failure	17 (8.9)	18 (8.8)	
	Indeterminate	21 (11.0)	10 (4.9)	

Source: Reviewer Table

Treatment Imbalances in Trial -08&09

In addition to potential treatment imbalances resulting from the pooling subjects from Protocol -08 and -09, imbalances can also result from the primary analysis population in Trial -08&09 being defined as a subgroup of randomized patients (i.e. MITT subjects). Based on prognostic factors at baseline (previously shown in **Table 5**), further exploratory analyses were conducted to compare treatment arms by potential risk factors which were identified as showing the lowest clinical cure rates across all subjects (i.e. combined treatment arms), **Figure 5**.

Reviewer Comments: *Pooling of subjects from the -08 and -09 protocols and defining the MITT (a subgroup of the ITT) as the primary analysis population were both agreed to by the Agency at the design stage. However, such design features may have limitations with respect to optimally balancing treatments by important baseline risk factors (e.g. stratification factors). For example, although the initial randomization of ITT subjects in Trial -08&-09 was stratified by study site, some imbalances in the MITT population were observed for the region variable,* ***Table 5****.*

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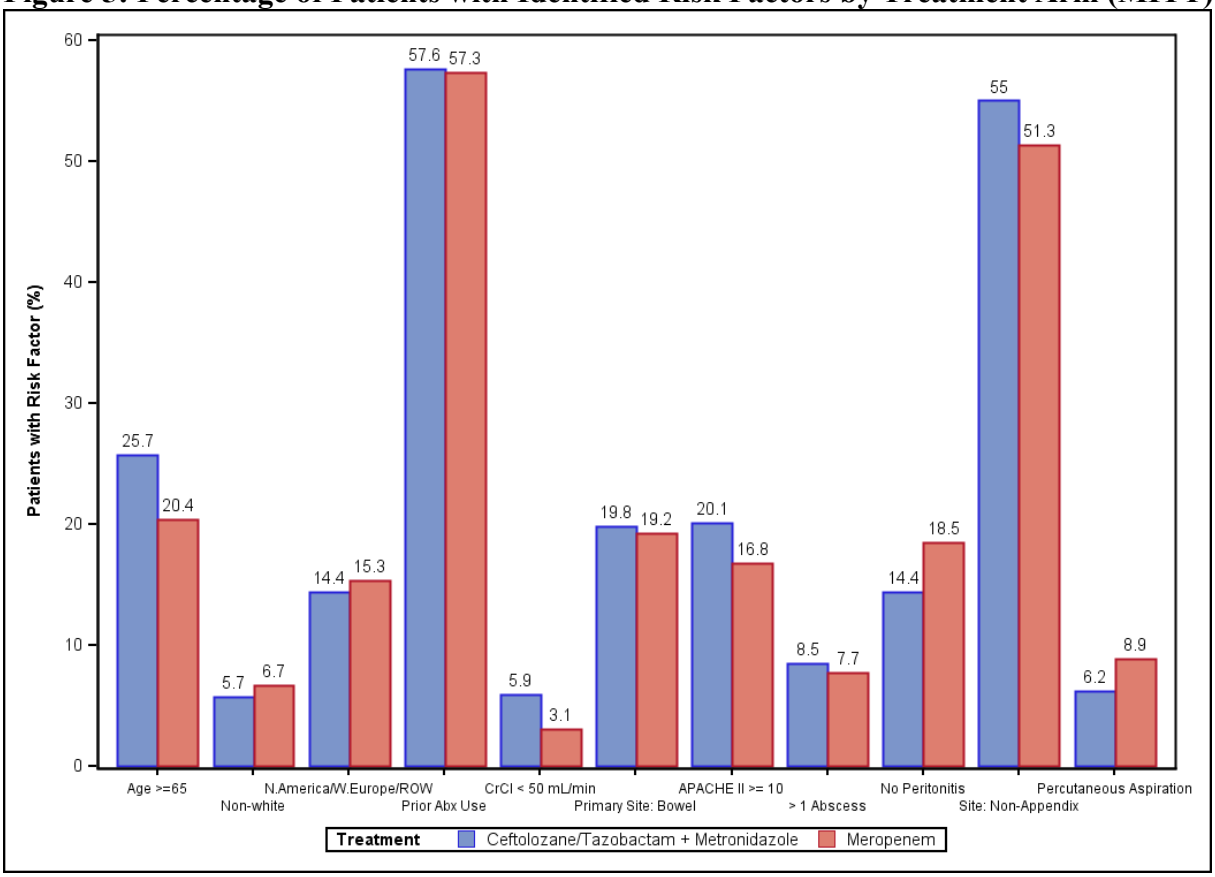
Although this can lead to potential confounding in the primary analysis, findings from Reviewer sensitivity analyses which adjusted for major risk factors (e.g. stratification factors) showed findings which were similar to those of the primary analysis, ***Table 17****.*

In **Figure 5**, there appeared to be some imbalances between the two treatment arms. However, these imbalances did not appear to favor the ceftolozane/tazobactam + metronidazole arm which showed similar or slightly higher percentages of patients with these 11 risk factors.

Figure 5: Percentage of Patients with Identified Risk Factors by Treatment Arm (MITT)



Source: Reviewer Figure

Reviewer Comments: *'Creatinine clearance < 50 ml/min at baseline' was a strong risk factor which was not well balanced between the treatment arms. However, there were a larger percentage of patients in the ceftolozane/tazobactam + metronidazole arm with this risk factor at 5.9% vs. 3.1% which would likely lead to more conservative findings. Patients with creatinine clearance < 50 ml/min had clinical cure rates of 11/23 (47.8%) in the ceftolozane/tazobactam + metronidazole arm and 9/13 (69.2%) in the meropenem arm.*

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Multivariate Logistic Regression Analyses

The Reviewer conducted multivariate regression analyses in the MITT population to explore whether specific risk factors in the presence of all other model factors may be driving the less favorable clinical responses (cure/failure) that were observed in the ceftolozane/tazobactam + metronidazole arm, especially in high risk populations. The Reviewer also requested that the Applicant conduct the same multivariate regression analyses.

In the multivariate regression analysis, the risk factors (explanatory variables) included treatment (ceftolozane/tazobactam + metronidazole, meropenem), age group (< 65, ≥ 65), prior antibiotics (Yes, No), Renal function, CrCl (< 50, ≥ 50 mL/min), primary site of infection (bowel, other), APACHE II Score (< 10, ≥ 10), Number of Abscesses (≤ 1, < 1), Peritionitis (Local, Diffuse, None), Anatomic Site of Infection (Appendix, Non-appendix), Region (N. America, S. America, E. Europe, W. Europe and Rest of World). A second model considered the same risk factors as the above model above except that it excluded the Region variable.

Reviewer and Applicant results of these multivariate logistic regressions showed coefficients for most of these risk factors were at or near significance (i.e. significantly different from 0). The most significant factor appeared to be creatinine clearance which may possibly be driving the findings. However, the influence of other risk factors did not appear to be conclusive. Note that these multivariate logistic regression analyses were exploratory and did not attempt to draw inferences. These analyses also had several limitations relating to the post-hoc nature of the testing (e.g. inflation of the overall type I error rate), model selection criteria (e.g. selection biases in including/excluding potential explanatory variables), power (esp. in smaller subgroups), and model assessment (e.g. unclear adequacy and reliability of model).

5. SPECIAL/SUBGROUP POPULATIONS

5.1 Subgroup Analyses by Age, Gender, Race, Geographic Region

Table 23 shows subgroup analyses of clinical cure rates at TOC in the MITT population by age, gender, race and geographic region. In comparisons across all subjects (i.e. combined treatment arms), clinical cure rates were lower in patients who were ≥ 65 years, non-white or from the region of North America/Western Europe/ROW. Treatment differences in clinical cure rates at TOC were less favorable in the ceftolozane/tazobactam + metronidazole arm for most of the subgroups including patients ≥ 65 years at -13.4% (95% CI: -25.1%, -0.8%), patients of white race at -5.3% (95% CI: -5.3%, -0.3%), patients from Eastern Europe at -5.0% (-10.2%, 0.0%). However, similar to the primary analysis, treatment differences were influenced by substantial differences in indeterminate outcomes which were counted as outcomes of failure.

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Table 23: Clinical Cure Rates at TOC by Age, Gender, Race, Region (MITT)

Subgroup Category	Assessment	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Difference (95% CI))
Age				
< 65		N=289	N=332	
	Cure	254 (87.9)	294 (88.6)	-0.7 (-5.9, 4.4)
	Failure	18 (6.2)	27 (8.1)	
	Indeterminate	17 (5.9)	11 (3.3)	
≥ 65		N=100	N=85	
	Cure	69 (69.0)	70 (82.4)	-13.4 (-25.1, -0.8)
	Failure	14 (14.0)	7 (8.2)	
	Indeterminate	17 (17.0)	8 (9.4)	
Gender				
Male		N=218	N=248	
	Cure	181 (83.0)	217 (87.5)	-4.5 (-11.1, 2.0)
	Failure	19 (8.7)	21 (8.5)	
	Indeterminate	18 (8.3)	10 (4.0)	
Female		N=171	N=169	
	Cure	142 (83.0)	147 (87.0)	-3.9 (-11.6, 3.7)
	Failure	13 (7.6)	13 (7.7)	
	Indeterminate	16 (9.4)	9 (5.3)	
Race				
White		N=367	N=388	
	Cure	306 (83.4)	344 (88.7)	-5.3 (-10.3, -0.3)
	Failure	29 (7.9)	29 (7.5)	
	Indeterminate	32 (8.7)	15 (3.9)	
Other		N=22	N=28[1]	
	Cure	17 (77.3)	19 (67.9)	9.4 (-15.7, 31.8)
	Failure	3 (13.6)	5 (17.9)	
	Indeterminate	2 (9.1)	4 (14.3)	

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Region				
North America		N=26	N=25	
	Cure	17 (65.4)	19 (76.0)	-10.6 (-33.5, 14.1)
	Failure	6 (23.1)	4 (16.0)	
	Indeterminate	3 (11.5)	2 (8.0)	
South America		N=36	N=45	
	Cure	34 (94.4)	41 (91.1)	3.3 (-10.4, 15.8)
	Failure	2 (5.6)	3 (6.7)	
	Indeterminate	0	1 (2.2)	
E. Europe		N=297	N=308	
	Cure	256 (86.2)	281(91.2)	-5.0 (-10.2, 0.0)
	Failure	14 (4.7)	17 (5.5)	
	Indeterminate	27 (9.1)	10 (3.2)	
W. Europe		N=11	N=19	
	Cure	5 (45.5)	10 (52.6)	-7.2 (-38.6, 26.6)
	Failure	5 (45.5)	7 (36.8)	
	Indeterminate	1 (9.1)	2 (10.5)	
Rest of World		N=19	N=20	
	Cure	11 (57.9)	13 (65.0)	-7.1 (-34.5, 21.7)
	Failure	5 (26.3)	3 (15.0)	
	Indeterminate	3 (15.8)	4 (20.0)	
N.America/ W.Europe/ ROW[2]		N=56	N=64	
	Cure	33 (58.9)	42 (65.6)	-6.7 (-23.4, 10.4)
	Failure	16 (28.6)	14 (21.9)	
	Indeterminate	7 (12.5)	8 (12.5)	

[1] One patient in the meropenem arm had missing data for race.
[2] Includes North America, Western Europe and Rest of World. Identified as potential risk factor in **Figure 5**.
Source: Reviewer Table

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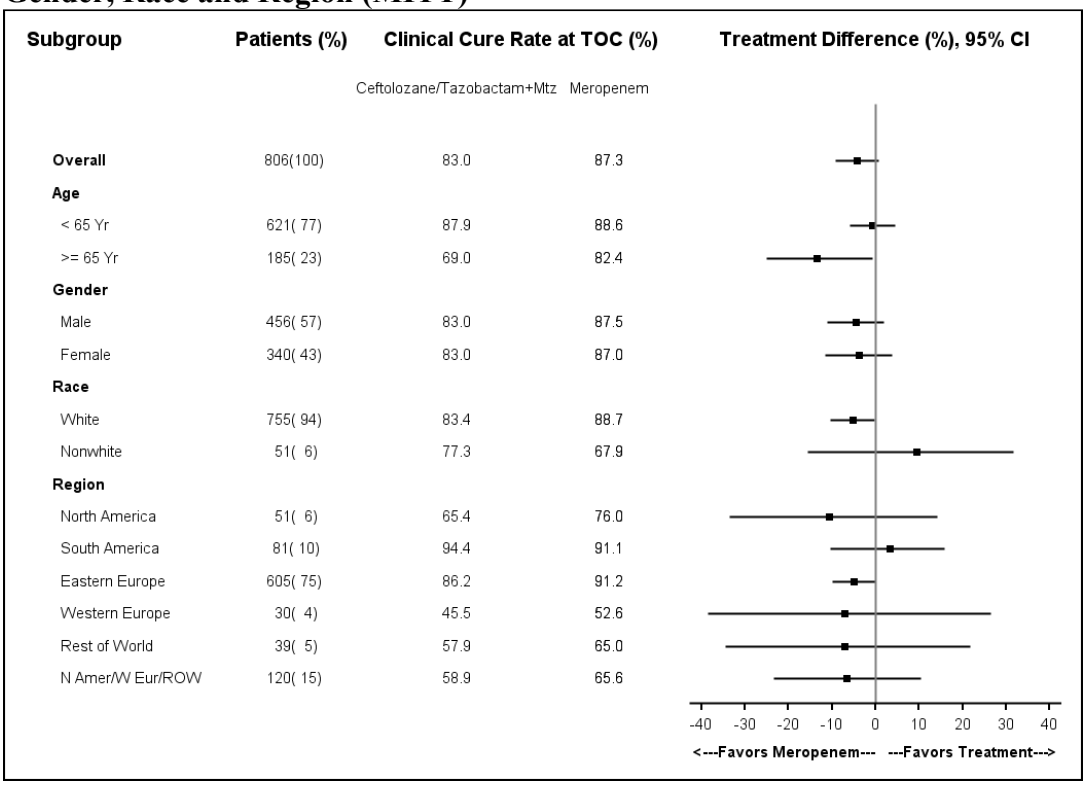
Figure 6: Forest Plot of Treatment Differences in Clinical Cure Rates at TOC by Age, Gender, Race and Region (MITT)



'Mtz' denotes metronidazole.
Source: Reviewer Figure

Reviewer Comments: *Due to the large percentage of MITT patients who were white (94%) or from Eastern Europe (75%), comparisons in other races (i.e. non-white) or other regions (i.e. North America, South America, Western Europe, Rest of World) were limited by small numbers.*

5.2 Other Special/Subgroup Populations

Subgroup Analyses by Other Baseline Prognostic Factors

Table 24 shows analyses of clinical cure rates at TOC in the MITT population by other baseline prognostic factors which included primary site of infection, anatomic site of infection, prior antibiotic use, APACHE II Scores, creatinine clearance, number of abscesses, peritonitis, procedure and number of pathogens. In comparisons across all subjects (combined treatment arms), cure rates were lower in patients with the following baseline risk factors: the primary site of infection in the bowel, anatomic site of non-appendix, use of prior antibiotics, APACHE II Scores ≥ 10, creatinine clearance < 50 mL/min, multiple abscesses, an infection not involving peritonitis and a procedure of percutaneous aspiration.

In treatment comparisons, differences in clinical cure rates at TOC were less favorable in ceftolozane/tazobactam + metronidazole patients with higher risk profiles at baseline: patients ≥ 65 years or from N.America/W.Europe/ROW (**Table 23**) or with primary site of infection in the bowel, anatomic site of infection of non-appendix, prior antibiotics use, creatinine clearance < 50 mL/min, APACHE II Scores ≥ 10, multiple abscesses or a percutaneous aspiration procedure (**Table 24**). However, as in the primary analysis, treatment differences were influenced by indeterminate outcomes which were counted as outcomes of failure in these subgroup analyses. Such an influence was most pronounced in the comparison of patients with creatinine clearance < 50 mL/min in which 9/23 (39.1%) of patients in the ceftolozane/tazobactam + metronidazole had indeterminate outcomes vs. 1/13 (7.7%) in the meropenem arm.

Reviewer Comments: *Treatment differences were also less favorable in ceftolozane/tazobactam + metronidazole patients having a laparotomy, diffuse peritonitis or a polymicrobial infection. However, these prognostic variables were not associated with a higher risk profile.*

Table 24: Clinical Cure Rates at TOC by Other Baseline Prognostic Factors (MITT)

Subgroup Category	Clinical Response	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Difference (95% CI)
Primary Site of Infection[1]				
Bowel (small or large)		N=77	N=80	
	Cure	53 (68.8)	63 (78.8)	-9.9 (-23.3, 3.8)
	Failure	13 (16.9)	11 (13.8)	
	Indeterminate	11 (14.3)	6 (7.5)	
Other Site		N=312	N=337	
	Cure	270 (86.5)	301 (89.3)	-2.8 (-7.9, 2.3)
	Failure	19 (6.1)	23 (6.8)	
	Indeterminate	23 (7.4)	13 (3.9)	
Anatomic Site of Infection				
Appendix		N=179	N=205	
	Cure	160 (89.4)	189 (92.2)	-2.8 (-8.9, 3.0)
	Failure	8 (4.5)	11 (5.4)	
	Indeterminate	11 (6.1)	5 (2.4)	
Non-appendix		N=210	N=212	
	Cure	163 (77.6)	175 (82.5)	-4.9 (-12.5, 2.7)
	Failure	24 (11.4)	23 (10.8)	
	Indeterminate	23 (11.0)	14 (6.6)	
Use of Prior Antibiotics				
Yes		N=224	N=239	
	Cure	176 (78.6)	201 (84.1)	-5.5 (-12.7, 1.6)
	Failure	27 (12.2)	26 (10.9)	
	Indeterminate	21 (9.5)	12 (5.0)	

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No		165	178	
	Cure	147(89.1)	163 (91.6)	-2.5 (-9.0, 3.9)
	Failure	5 (3.0)	8 (4.5)	
	Indeterminate	13 (7.9)	7 (3.9)	
APACHE II Score[2]				
< 10		N=310	N=347	
	Cure	268 (86.5)	308 (88.8)	-2.3 (-7.5, 2.7)
	Failure	20 (6.5)	26 (7.5)	
	Indeterminate	22 (7.1)	13 (3.7)	
≥ 10		N=78	N=70	
	Cure	54 (69.2)	56 (80.0)	-10.8 (-24.2, 3.4)
	Failure	12 (15.4)	8 (11.4)	
	Indeterminate	12 (15.4)	6 (8.6)	
Creatinine Clearance (mL/min)				
< 50		N=23	N=13	
	Cure	11 (47.8)	9 (69.2)	-21.4 (-47.3, 11.6)
	Failure	3 (13.0)	3 (23.1)	
	Indeterminate	9 (39.1)	1 (7.7)	
≥ 50		N=366	N=404	
	Cure	312 (85.2)	355 (87.9)	-2.6 (-7.5, 2.2)
	Failure	29 (7.9)	31 (7.7)	
	Indeterminate	25 (6.8)	18 (4.5)	
Number of Abscesses				
No Abscess		N=170	N=177	
	Cure	142 (83.5)	155 (87.6)	-4.0 (-11.6, 3.4)
	Failure	9 (5.3)	14 (7.9)	
	Indeterminate	19 (11.2)	8 (4.5)	
Single		N=186	N=208	
	Cure	157 (84.4)	183 (88.0)	-3.6 (-10.6, 3.3)
	Failure	18 (9.7)	15 (7.2)	
	Indeterminate	11 (5.9)	10 (4.8)	
Multiple		N=33	N=32	
	Cure	24 (72.7)	26 (81.3)	-8.5 (-28.1,12.1)
	Failure	5 (15.2)	5 (15.6)	
	Indeterminate	4 (12.1)	1 (3.1)	
Peritonitis Type				
No peritonitis		N=52	N=77	
	Cure	40 (76.9)	62 (80.5)	-3.6 (-18.6, 10.3)
	Failure	8 (15.4)	11 (14.3)	
	Indeterminate	4 (7.7)	4 (5.2)	

Reference ID: 3652150

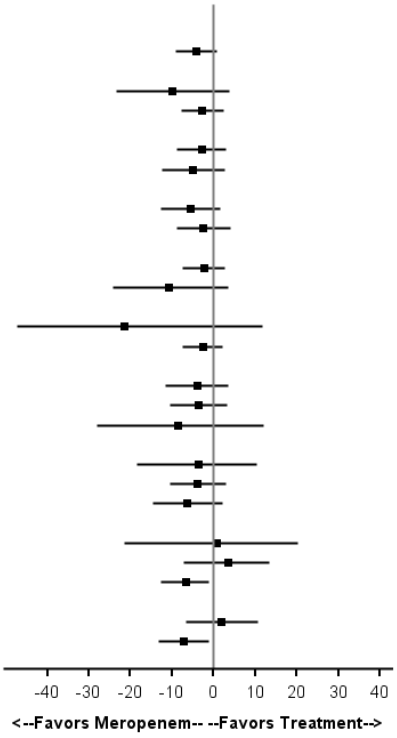
Local		N=198	N=203	
	Cure	168 (84.8)	180 (88.7)	-3.8 (-10.6, 2.9)
	Failure	12 (6.1)	13 (6.4)	
	Indeterminate	18 (9.1)	10 (4.9)	
Diffuse		N=139	N=137	
	Cure	115 (82.7)	122 (89.1)	-6.3 (-14.6, 2.0)
	Failure	12 (8.6)	10 (7.3)	
	Indeterminate	12 (8.6)	5 (3.6)	
Procedure Type				
Percutaneous Aspiration		N=24	N=37	
	Cure	19 (79.2)	29 (78.4)	0.8 (-21.4, 20.2)
	Failure	5 (20.8)	6 (16.2)	
	Indeterminate	0	2 (5.4)	
Laparoscopy		N=86	N=105	
	Cure	75 (87.2)	88 (83.8)	3.4 (-7.1, 13.3)
	Failure	5 (5.8)	12 (11.4)	
	Indeterminate	6 (7.0)	5 (4.8)	
Laparotomy		N=274	N=271	
	Cure	228 (83.2)	244 (90.0)	-6.8 (-12.6, -1.1)
	Failure	19 (6.9)	16 (6.3)	
	Indeterminate	27 (9.9)	11 (4.0)	
Other		N=5	N=4	
	Cure	1 (20.0)	3 (75.0)	-55.0 (-81.2, 6.8)
	Failure	3 (60.0)	0	
	Indeterminate	1 (20.0)	1 (25.0)	
Number of Baseline Pathogens				
Monomicrobial Infection		N=132	N=129	
	Cure	114 (86.4)	109 (84.5)	1.9 (-6.8, 10.6)
	Failure	10 (7.6)	10 (7.8)	
	Indeterminate	8 (6.1)	10 (7.8)	
Polymicrobial Infection		N=257	N=288	
	Cure	209 (81.3)	255 (88.5)	-7.2 (-13.3, -1.2)
	Failure	22 (8.6)	24 (8.3)	
	Indeterminate	26 (10.1)	9 (3.1)	

[1] Primary site of infection is as recorded on the eCRF
[2] One patient in the ceftolozane/tazobactam + metronidazole arm did not have an APACHE II assessment.
Source: Reviewer Table

Reference ID: 3652150

Figure 7: Forest Plot of Clinical Cure Rates by Other Baseline Prognostic Factors (MITT)

Subgroup	Patients (%)	Clinical Cure Rate at TOC (%)	
		Ceftolozane/Tazobactam+Mtz	Meropenem
Overall	806(100)	83.0	87.3
Primary Site of Infection			
Bowel	157(19)	68.8	78.8
Other Site	649(81)	86.5	89.3
Anatomic Site of Infection			
Appendix	384(48)	89.4	92.2
Non-Appendix	422(52)	77.6	82.5
Prior Antibiotic Use			
Yes	463(57)	78.6	84.1
No	343(43)	89.1	91.6
Apache II Score			
< 10	657(82)	86.5	88.8
>=10	148(18)	69.2	80.0
Creatinine Clearance			
<50 mL/min	36(4)	47.8	69.2
>=50 mL/min	770(96)	85.2	87.9
Number of Abscesses			
No Abscess	347(43)	83.5	87.6
Single	394(49)	84.4	88.0
Multiple	65(8)	72.7	81.3
Peritonitis Type			
No Peritonitis	129(16)	76.9	80.5
Local	401(50)	84.8	88.7
Diffuse	286(35)	82.7	89.1
Procedure Type			
Percutaneous Aspiration	61(8)	79.2	78.4
Laparoscopy	191(24)	87.2	83.8
Laparatomy	545(68)	83.2	90.0
Number of Pathogens			
Monomicrobial Infection	261(32)	86.4	84.5
Polymicrobial Infection	545(68)	81.3	88.5



There were 9 Patients with procedure type of 'Other' not included above. 'Mtz' denotes metronidazole.
Source: Reviewer Figure

6. SUMMARY AND CONCLUSIONS

6.1 Statistical Issues and Findings

Issues related to study design & conduct, analyses and results are summarized below:

Study Design & Conduct

- Trial -08&09 pooled subjects from two individual Phase 3 trials (i.e. Trial -08 and Trial -09) which may have inherent differences in the variability of the primary outcome as well as the distribution of confounding factors.
- The primary analysis of Trial -08&09 was a subgroup analysis of randomized patients (i.e. the MITT population). In a pooled analysis of such subgroups, treatments may not be adequately balanced with respect to confounding variables.

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Study Results

- The primary analysis of clinical cure rates at Test-of-Cure (TOC) on Day 24-32 in the MITT showed a treatment difference (ceftolozane/tazobactam plus metronidazole minus meropenem) of -4.3% (95% CI: -9.2%, 0.7%). This finding met non-inferiority based on the lower confidence limit of -9.2% which fell slightly above the pre-specified NI margin of -10%.
- Subgroup analyses suggested a possible trend towards less favorable efficacy outcomes in the ceftolozane/tazobactam + metronidazole arm in patients with higher risk profiles at baseline (e.g. age ≥ 65 years, APACHE II Score > 10, creatinine clearance < 50 mL/min., multiple abscesses).
- Similar to the efficacy analyses, safety analyses also tended to be less favorable in the treatment arm. When pooling subjects from Trial -08&09 and Trial CXA-IAI-10-01, all-cause mortality rates were 2.5% in the ceftolozane/tazobactam + metronidazole arm compared to 1.5% in the meropenem arm, an adjusted difference of 1.0% (95% CI: -0.9%, 2.8%). Rates for most commonly reported adverse reactions in Trial -08&09 also tended to be higher in the ceftolozane/tazobactam + metronidazole arm.

6.2 Collective Evidence

This review primarily considers findings provided from Trial -08&09. Although efficacy findings from the Phase 2 trial, Trial -01, could be observed and were found to be less favorable in the ceftolozane/tazobactam + metronidazole than in the meropenem arm (Appendix **Table 25**), they could not be pooled with findings from Trial -08&09 due to various design differences. For example, compared to Trial -08&09, Trial -01 had a shorter duration of study therapy and earlier timing of the primary assessment. Trial -01 was also limited in sample size, including only N=86 modified micro-ITT (mMITT) subjects.

However, safety analyses of all-cause mortality rates could be performed across Trials -01 and -08&09 . These comparisons showed higher mortality rates in the ceftolozane/tazobactam than in the meropenem arm at 14/564 (2.5%) vs. 8/545(1.5%). Adjusting for the size of the trials, the weighted treatment difference was 1.0% (95% CI: -0.9%, 2.8%).

6.3 Conclusions and Recommendations

Study -08&09 provided adequate evidence to support the use of ceftolozane/tazobactam in treating adults with cIAI based on non-inferiority comparisons of clinical cure rates at TOC which met the pre-specified margin. However, the Reviewer's sensitivity and subgroup analyses showed a trend towards less favorable treatment differences in the ceftolozane/tazobactam + metronidazole arm across a broad range of conditions, especially in patients with higher risk profiles.

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As a post-marketing commitment, the reviewer recommends that the Applicant conduct an additional adequate and well controlled study in higher risk patients with substantially lower expected clinical cure rates (e.g. patients with creatinine clearance < 50 mL/min).

6.4 Labeling Recommendations

Labeling negotiations are still ongoing. However, some of the major changes based on statistical recommendations made to the Applicant's initially proposed labels included the following:

- Primary and secondary analysis results presented with unstratified Wilson Score CIs.

  Reviewer Comments*: This recommendation was made due to concerns with the reliability of the Applicant's pre-specified approach of* [redacted] (b) (4) *As discussed previously, an unstratified approach provided conservative results and was the Applicant's pre-specified primary analysis approach,* [redacted] (b) (4).

- The recommendation to remove clinical cure rates (by pathogen) in [redacted] (b) (4) and replace with rates in the MITT population.

  Reviewer Comments: The *MITT was considered to be more informative.* [redacted] (b) (4)

7. REFERENCES

1. US Department of Health and Human Services. Food and Drug Administration Guidance for Industry. Complicated intra-abdominal infections: developing drugs for treatment. September 2012.
2. Mehrotra DV, Railkar R. Minimum risk weights for comparing treatment in stratified binomial trials. Stat Med 2000Mar 30; 19:811-25.
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8. APPENDIX

Trial -01 (Phase 2 trial)

In **Table 25**, treatment differences in Trial -01 for the modified micro-ITT (mMITT) and ME co-primary populations were less favorable in the ceftolozane/tazobactam + metronidazole arm at -12.4% (95% CI: -24.1, 4.8) and -7.2% (-18.9, 10.0), respectively. Point estimates were unfavorable as well as limited by the small sample sizes, especially in the meropenem arm.

Table 25: Trial -01: Clinical Response at TOC (mMITT & ME Co-Primary Populations)

	Ceftolozane/ Tazobactam + Metronidazole n (%)	**Meropenem** n (%)	**Difference (95% CI)**
mMITT Population	**N=61**	**N=25**	
Clinical Cure Rate	51 (83.6)	24 (96.0)	-12.4% (-24.1, 4.8)
Clinical Failure Rate	6 (9.8)	1 (4.0)	
Indeterminate	4 (6.6)	0 (0.0)	
ME Population	**N=53**	**N=24**	
Clinical Cure Rate	47 (88.7)	23 (95.8)	-7.2% (-18.9, 10.0)
Clinical Failure Rate	6 (11.3)	1 (4.2)	

Source: Reviewer Analysis

Table 26 shows clinical cure rates at TOC by baseline pathogen in the expanded ME population. Cure rates were generally similar across both treatment arms. Lower cure rates in ceftolozane/tazobactam + metronidazole patients with *S. anginosus* at baseline were noted at 25/30 (83.3%) vs. 23/23 (100%).

Table 26: Clinical Cure Rates at TOC in Trial -08&09 by Pathogen (Expanded ME)

Organism Group Pathogen	**Ceftolozane/ Tazobactam + Metronidazole (N=307) n/N (%)**	**Meropenem (N=345) n/N (%)**
Aerobic Gram-negative	238/252 (94.4)	273/291 (93.8)
Escherichia coli	197/208 (94.7)	216/231 (93.5)
Klebsiella pneumonia	28/30 (93.3)	22/25 (88.0)
Pseudomonas aeruginosa	26/26 (100)	27/29 (93.1)
Enterobacter cloacae	19/22 (86.4)	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	153/168 (91.1)	170/185 (91.9)
Streptococcus anginosus	25/30 (83.3)	23/23 (100)

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Organism Group Pathogen	Ceftolozane/ Tazobactam + Metronidazole (N=307) n/N (%)	Meropenem (N=345) n/N (%)
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)
Bacteroides thetaiotaomicron	20/20 (100)	40/43 (93.0)
Bacteroides vulgatus	12/13 (92.3)	21/22 (95.5)

Source: Reviewer Table

Table 27 shows clinical cure rates at TOC in the ITT and expanded ME populations. Findings in these populations were less favorable in the ceftolozane/tazobactam + metronidazole arm, however differences were less pronounced than in the primary MITT analysis.

Table 27: Clinical Response at TOC in Other Analysis Populations

Clinical Response	Ceftolozane/ Tazobactam + Metronidazole n/N (%)	Meropenem n/N (%)	Difference (95% CI)
ITT Patients	N=487	N=506	
Cure	407 (83.6)	436 (86.2)	-2.6% (-7.1, 1.9)
Failure	36 (7.4)	36 (7.1)	
Indeterminate	44 (9.0)	34 (6.7)	
Expanded ME Population	N=307	N=345	
Cure	288 (93.8)	323 (93.6)	0.2% (-3.7, 4.0)
Failure	19 (6.2)	22 (6.4)	

[1] 95% CI calculated as unstratified Wilson Score CIs.
[2] Clinical Response at TOC in MITT (primary) and ME (secondary) analysis populations is provided in **Table 6.**
Source: Reviewer Table

Use of Prior Antibiotics

Additional analyses characterized the dosage and duration of recent use of prior antibiotics (i.e. within 72 hours of the initiation of study drug), **Table 28**. Subgroup analyses considered clinical cure rates by prior antibiotic use and by timing (i.e. before vs. after initial surgery), **Table 29**. Treatment differences in clinical cure rates in patients using prior antibiotics were more pronounced than in patients not using prior antibiotics use at -4.4% (95% CI: -11.6%, 2.7%) vs. -4.1% (-10.7%, 2.3%). This suggests that the use of prior antibiotics is unlikely to substantially affect primary analysis findings in favor of the ceftolozane/tazobactam + metronidazole arm. In **Table 29,** further subgroup analyses showed less favorable treatment differences in

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ceftolozane/tazobactam + metronidazole patients receiving prior antibiotics after the initial procedure. However, inferences in this subgroup are limited by a small number of patients.

Table 28: Number (%) of Patients with Prior Antibiotic Therapy by Duration of Therapy and Number of Doses (MITT)

Clinical Response	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Total (N=806) n (%)
Prior Antibiotic Therapy[1]	218 (56.0)	234 (56.1)	452 (56.1)
Duration of Therapy[2]			
≤ 24 hours	196 (50.4)	211 (50.6)	407 (50.5)
> 24 hours	21 (5.4)	22 (5.3)	43 (5.3)
Number of Doses[2,3]			
Single	139 (35.7)	142 (34.1)	281 (34.9)
Multiple	75 (19.3)	90 (21.6)	165 (20.5)

[1] Prior Antibiotic Use had to be within 72 hours of initiation of study therapy
[2] 2 patients with prior antibiotic therapy (1 per arm) had missing values for duration of therapy
[3] 4 ceftolozane/tazobactam + metronidazole and 2 meropenem patients had a missing duration or number of doses
[4] Patients with > 24 hours of prior antibiotic therapy are assumed to have multiple doses
Source: Reviewer Table

Table 29: Clinical Cure Rates by Prior Antibiotic Use Relative to Initial Procedure (MITT)

Subgroup by Prior Antibiotics Use	Ceftolozane/ Tazobactam + Metronidazole (N=389) n (%)	Meropenem (N=417) n (%)	Difference (95% CI)
Prior Antibiotics[1]	**N=218**	**N=234**	
Clinical Cure	173 (79.4)	196 (83.8)	-4.4 (-11.6, 2.7)
Failure	45 (20.6)	38 (16.2)	
Prior Antibiotics Before Procedure	**N=179**	**N=201**	
Clinical Cure	143 (79.9)	168 (83.6)	-3.7 (-11.6, 4.1)
Failure	36 (20.1)	32 (16.4)	
Prior Antibiotics After Procedure	**N=38**	**N=32**	
Clinical Cure	29 (76.3)	28 (87.5)	-11.2 (-28.4, 7.7)
Failure	9 (23.7)	4 (12.5)	
No Prior Antibiotics	**N=171**	**N=183**	
Clinical Cure	150 (87.7)	168 (91.8)	-4.1 (-10.7, 2.3)
Failure	21 (22.3)	15 (8.2)	

[1] Prior Antibiotic Use had to be within 72 hours of initiation of study therapy.
Source: Reviewer Table

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SIGNATURES/DISTRIBUTION LIST

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Date: 10/31/2014

Concurring Reviewers: Thamban Valappil, Ph.D., Statistical Team Leader
Dionne Price, Ph.D., Division Director

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10/31/2014

THAMBAN I VALAPPIL
10/31/2014
NDA Review

DIONNE L PRICE
11/10/2014
Concur with overall conclusion of efficacy/safety.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISICAL REVIEW AND EVALUATION

DIVISION DIRECTOR MEMO

NDA:	206829
Drug Name:	Zerbaxa (ceftolozane/tazobactum)
Applicant:	Cubist Pharmaceuticals, Inc
Indication:	Complicated urinary tract infections
Project manager:	Maureen Dillon Parker
Clinical team:	Medical officers: Maria Allende, Hala Shamsuddin Clinical team leader: Thomas Smith
Dates:	Stamp date: April 21, 2014 PDUFA date: December 21, 2014
Statistical reviewer:	Dan Rubin
Statistics team leader:	Thamban Valappil

In Dr. Rubin's review of NDA 206829, he expressed some concern with the components of the composite primary endpoint. In my opinion, the concerns may need to be discussed among a broader internal group in the setting of overall recommendations for development programs targeting complicated urinary tract infections.

For the current review, Dr. Rubin acknowledged that the design and analyses were generally in agreement with the *Guidance for Industry Complicated Urinary Tract Infections: Developing Drugs for Treatment (2012)*. I concur with Dr. Rubin's overall conclusion that the applicant has provided evidence of an effect of ceftolozane/tazobactum for the treatment of complicated urinary tract infections.

Reference ID: 3639478

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DIONNE L PRICE
10/04/2014

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 206829
Drug Name:	Zerbaxa (ceftolozane/tazobactam) injection for intravenous use
Indication(s):	Complicated urinary tract infections
Applicant:	Cubist Pharmaceuticals, Inc.
Date(s):	Stamp date: April 21, 2014
	PDUFA date: December 21, 2014
Review Priority:	Priority review
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Daniel Rubin
Concurring Reviewers:	Statistical Team Leader: Thamban Valappil
	Division Director: Dionne Price
Medical Division:	Division of Anti-Infective Products
Clinical Team:	Medical Officer: Maria Allende
	Medical Officer: Hala Shamsuddin
	Clinical Team leader: Thomas Smith

Keywords: Active control/non-inferiority, clinical studies, combination drug, NDA review, subgroup analyses, subjective outcomes, treat-by-baseline interaction.

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1 EXECUTIVE SUMMARY

In this submission the Applicant, Cubist Pharmaceuticals, seeks to provide evidence that ceftolozane/tazobactam is safe and effective for the treatment of complicated urinary tract infections (cUTIs). The drug is the combination of ceftolozane, a new antibiotic in the cephalosporin class, and tazobactam, an FDA-approved beta-lactamase inhibitor that does not itself possess antibacterial activity but is meant to counter bacterial resistance mechanisms when combined with an antibiotic.

The Applicant conducted a Phase 3 trial in subjects with cUTIs and a trial in subjects with complicated intra-abdominal infections (cIAIs). Results in these trials were meant to provide corroborative evidence of safety and efficacy, even though the drug was used for infections at different sites in the body. The focus of this review is the cUTI study.

The cUTI trial was a randomized, double-blind trial that enrolled 1083 total patients. Subjects with signs and symptoms of a complicated urinary tract infection were randomized in a 1:1 ratio to either intravenously administered ceftolozane/tazobactam or intravenously administered levofloxacin, an antibiotic in the quinolone class that is FDA-approved for treating cUTIs. The primary analysis population was the modified microbiological intention-to-treat population (mMITT) comprised of all randomized subjects who received any amount of study drug and had a microbiologically confirmed infection from a specimen taken prior to study drug administration. Subjects were treated for 7 days with intravenous therapy, without provisions for a switch to oral therapy. The primary efficacy endpoint was a composite requiring both investigator judgment that signs and symptoms had resolved and microbiological eradication of the causative pathogen by the test of cure (TOC) visit 7 ± 2 days following the end of therapy. The trial was designed to evaluate non-inferiority, specifically whether the difference in success rates between ceftolozane/tazobactam and levofloxacin exceeded 10%.

Subjects in the mMITT primary efficacy analysis population were 74% female, 82% had pyelonephritis, 8% had concurrent bacteremia, 76% were enrolled in Eastern Europe, and 79% were infected by *Escherichia coli* at baseline. Only 14 subjects (2%) in the mMITT population were enrolled in the United States, potentially limiting the generalizability to US patients.

Although designed to evaluate non-inferiority, Table 1 shows that ceftolozane/tazobactam met statistical criteria for demonstrating superiority relative to the levofloxacin control with respect to the primary efficacy analysis.

The likely reason for the superiority demonstration was that 212 subjects (27%) in the primary mMITT population had baseline pathogens resistant to levofloxacin, which as noted was the active control drug. Table 1 illustrates that ceftolozane/tazobactam led to better clinical and microbiological results than the control in the subgroup resistant to levofloxacin, and led to similar results in the group without levofloxacin resistance.

Table 1: Reviewer's summary of efficacy results

mMITT subgroup	TOC Outcome	Ceftolozane/ tazobactam	Levofloxacin	Difference (95% CI)
Entire mMITT	Composite cure	306/398 (76.9)	275/402 (68.4)	8.5 (2.3 to 14.6)
	Clinical cure	366/398 (92.0)	356/402 (88.6)	3.4 (-0.7 to 7.6)
	Microbiological success	320/398 (80.4)	290/402 (72.1)	8.3 (2.4 to 14.1)
Subset with levofloxacin resistance	Composite cure	60/100 (60.0)	44/112 (39.3)	20.7 (7.3 to 33.4)
	Clinical cure	90/100 (90.0)	86/112 (76.8)	13.2 (3.2 to 23.2)
	Microbiological success	63/100 (63.0)	49/112 (43.8)	19.2 (5.8 to 32.0)
Subset without levofloxacin resistance	Composite cure	246/298 (82.6)	231/290 (79.7)	2.9 (-3.4 to 9.3)
	Clinical cure	276/298 (92.6)	270/290 (93.1)	-0.5 (-4.8 to 3.8)
	Microbiological success	257/298 (86.2)	241/290 (83.1)	3.1 (-2.7 to 9.0)

This reviewer found that the results were robust to the handling of missing and indeterminate outcomes.

Although the superiority finding provided relatively direct and interpretable evidence for a treatment effect of ceftolzoane/tazobactam on investigator-judged clinical resolution and on microbiological eradication, the trial results did not provide statistical evidence of superior symptomatic improvement or a superior safety profile for ceftolozane/tazobactam, even in the subgroup resistant to the levofloxacin comparator.

(b) (4)

2 INTRODUCTION

2.1 Overview

The Applicant, Cubist Pharmaceuticals, has submitted a New Drug Application (NDA) seeking authorization to market ceftolozane/tazobactam for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI).

Originally, the Applicant initiated two confirmatory cUTI trials and two confirmatory cIAI trials to provide replicated evidence of safety and efficacy. However, following revised guidance from the Agency that one successful Phase 3 trial for cUTI and one successful Phase 3 trial for cIAI would provide supportive evidence for both indications the Applicant chose to conduct a single cUTI trial and a single cIAI trial. While blinded to results, the Applicant pooled the two ongoing cUTI studies into one trial, and likewise pooled two ongoing cIAI studies into one cIAI trial.

This review focuses on the evaluation of ceftolozane/tazobactam in the Phase 3 trial of patients with cUTI. Please refer to the statistical review of Christopher Kadoorie, Ph.D., for a discussion of the cIAI indication.

2.1.1 Complicated urinary tract infections (cUTI)

According to current FDA guidance documents to be subsequently discussed in this review, urinary tract infections are characterized by a documented microbial pathogen in the urine or blood along with pyuria (i.e., the presence of pus in the urine), and signs and symptoms of infection.

To be considered "complicated" an infection of the lower urinary tract or bladder (cLUTI) should be accompanied by an anatomical or functional abnormality such as catheterization, urinary retention, or obstructive uropathy. An infection of the upper urinary tract or kidney is termed pyelonephritis. Such cases are considered to be complicated irrespective of anatomical or functional abnormalities.

Infections that are not complicated are termed "uncomplicated urinary tract infections," and were not evaluated in this application. While uncomplicated infections predominately affect women, both men and women are affected by cUTIs.

According to the Applicant's Clinical Study Report and references therein, urinary tract infections account for approximately 100,000 hospital admissions annually in the United States and represent up to 40% of all hospital acquired infections.

A variety of different bacterial pathogens can cause cUTI, with the most common being *Escherichia coli* and other members of the Enterobacteriaceae family.

The treatment for cUTI is antibacterial therapy. Normally this is initiated in intravenous form, and patients can be discharged from the hospital and switched to oral antibacterial therapy after several days of successful treatment.

Antibacterial treatment for cUTI is typically initiated before the causative pathogen is known, because it can take between 48 to 72 hours to culture a pathogenic organism from a urine or blood sample and to test for susceptibilities to different antibiotics.

Antibacterial therapy for cUTI is meant to eradicate the bacterial pathogen and thereby resolve symptoms such as dysuria (painful urination), increased urinary frequency, increased urinary urgency, flank pain (i.e., abdominal pain), suprapubic pain, costobertebral angle tenderness (i.e., pain elicited by percussion of the lower back), nausea and vomiting, and fever and chills. With modern antibacterial therapies, cUTI is not typically life-threatening and does not typically lead to irreversible morbidity.

2.1.2 Ceftolozane/tazobactam

Ceftolozane/tazobactam is a combination product. Ceftolozane is an antibacterial drug within the antibiotic class known as cephalosporins. Like other cephalosporins, bacterial killing operates by inhibiting bacterial cell wall synthesis during cell wall division. The drug has shown *in vitro* activity against common cUTI pathogens including members of the Enterobacteriaceae family, as well as *Pseudomonas aeruginosa*. Ceftolozane is a new molecular entity that is not currently FDA-approved for any indication.

Tazobactam is a beta-lactamase inhibitor, meaning that by itself it does not directly kill or inhibit bacteria, but rather has utility in countering bacterial resistance mechanisms when used in combination with an antibiotic. Tazobactam is currently FDA-approved for treating a variety of infections when used in combination with piperacillin, an antibiotic in the penicillin class.

For more details regarding the drug's mechanism of action, this reviewer refers to the clinical microbiology review.

2.1.3 Hypothesis generating data and the Phase 2 program

This reviewer defers to the other respective review disciples for discussion of *in vitro* testing results, animal studies, pharmacokinetic and pharmacodynamic results, and the safety profile identified from Phase 1 studies in healthy volunteers.

Before initiating the confirmatory Phase 3 trial, the Applicant conducted a Phase 2 trial in subjects with cUTI. This study, numbered CXA-101-03, was a double-blind, randomized trial that compared intravenous ceftolozane to intravenous ceftazidime in a 7- to 10-day treatment regimen. Of note, ceftolozane was not combined with tazobactam in this trial. No switch to oral antibiotics was permitted. The trial randomized 86 subjects to the ceftolozane group and 43 subjects to the ceftazidime group. The primary efficacy endpoint was microbiological response 6 to 9 days after the end of therapy.

Among randomized subjects who received at least one dose of study drug and had a causative pathogen identified from a pre-treatment baseline urine specimen, microbiological response rates were 54/65 (83.1%) in the ceftolozane group and 29/38 (76.3%) in the ceftazidime group. The difference in response rates between groups did not reach statistical significance (p = 0.40).

The Applicant did not conduct inferential statistical analysis of this trial, but instead used descriptive statistics. This reviewer considers this Phase 2 trial to provide hypothesis generating results rather than substantial evidence of safety and efficacy.

2.1.4 FDA guidance document

The most recent FDA guidance document[1] on drug development for cUTI was released in February, 2012. The Applicant's final Phase 3 protocol was largely consistent with the guidance recommendations in terms of inclusion criteria, study assessments procedures, endpoints, and statistical analysis.

2.1.5 Regulatory history and pooling of studies

The relevant regulatory history and pooling of the Phase 3 cUTI trials can be described as follows in italicized text, taken from Section 9.8.2.1 of the Applicant's Clinical Study Report:

As part of the development program for ceftolozane/tazobactam, Cubist initiated 2 identical Phase 3 studies in cUTI, designated CXA-cUTI-10-04 and CXA-cUTI-10-05. Each of the pivotal cUTI protocols was identical even though approved under different protocol numbers.

In September 2012, the FDA released a new draft Guidance for Industry for Complicated Intra-Abdominal Infections stipulating a provision for "…a pathway that supports conducting a single study per indication for sponsors developing a drug for more than one indication for treatment of infections caused by similar bacterial pathogens.

Based on this guidance, and following agreement with the FDA and subsequently CHMP, Cubist revised its clinical development program for ceftolozane/tazobactam in both cUTI and cIAI indications to take advantage of the single-study approval pathway in each indication.

Consistent with this agreement with the agencies, Cubist completed each of the original studies (CXA-cUTI-10-04 and CXA-cUTI-10-05) separately, but subsequently pooled the data post-database lock prior to simultaneous unblinding, and then prepared 1 clinical study report for the cUTI indication.

[1] http://www.fda.gov/downloads/Drugs/Guidances/ucm070981.pdf. Accessed July 18, 2014.

With the exception of the location of the study sites, all study design features of the pivotal cUTI studies were identical although approved under different protocol numbers, ie, both protocols were double-blind, employed central randomization, were stratified by site, and had the same:

- *Inclusion and exclusion criteria;*
- *Primary efficacy variables;*
- *Drug dosing regimen;*
- *Comparator;*
- *Treatment duration;*
- *Outcome and safety assessments.*

Both protocols were also conducted in the same regions (although different counties, except for the United States and Russia, which were common for both studies).

2.1.6 Scope of review

Because this reviewer considered the Phase 2 results to be hypothesis generating, the originally designed Phase 3 cUTI trials were pooled into a single trial, and the Phase 3 cIAI trial in this application will be reviewed elsewhere by Christopher Kadoorie, Ph.D., this document focuses on the design and analysis of the single Phase 3 cUTI trial forged from pooling CXA-cUTI-10-04 and CXA-cUTI-10-05.

2.2 Data Sources

All datasets analyzed by this reviewer for the Phase 3 cUTI trial can be found at the following link in the Agency's Electronic Document Room: \\CDSESUB1\evsprod\NDA206829\0001\m5\datasets\cxa-cuti-10-04-10-05

In addition to patient-level datasets, other materials reviewed included the Applicant's protocol, statistical analysis plan, case report forms, and Clinical Study Report.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the submitted data for the Phase 3 cUTI trial was generally sufficient. This reviewer reproduced the Applicant's major efficacy and safety results from the submitted datasets without complex data manipulations. The analysis quality was also sufficient, as the Applicant's statistical analysis plans were precise and comprehensive. At of the time of this writing, this reviewer is not aware of inspection results from the Division of Scientific Investigations questioning the quality or integrity of the data. One issue of note was that the two countries with the highest enrollment were Russia and Ukraine, accounting for 160/1083 (14.8%) of randomized subjects, and sites in these countries could not be inspected by FDA personnel due to ongoing geopolitical tensions.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The Phase 3 cUTI trial considered in this review was a randomized, multicenter, double-blind, non-inferiority trial. The design overview in this section largely paraphrases from the Applicant's protocol and Clinical Study Report. The first subject in this trial was enrolled on July 28, 2011 and the last subject completed the trial on September 4, 2013.

3.2.1.1 Objectives

The Applicant reported the primary objective of the trial as follows: "*To demonstrate the noninferiority of ceftolozane/tazobactam versus comparator (levofloxacin) in adult subjects with cUTI (including pyelonephritis) based on the difference in composite microbiological eradication and clinical cure rate in the microbiological modified intent-to-treat (mMITT) population at the test-of-cure (TOC) visit (7 days [+/- 2 days] after last treatment) (ceftolozane/tazobactam minus comparator [levofloxacin]), using a noninferiority margin of 10%, at a 1-sided 0.025 significance level.*"

3.2.1.2 Inclusion and exclusion criteria

To participate in the trial subjects were required to be adults diagnosed with cUTI, which was defined as either an upper urinary tract infection (pyelonephritis) or a lower urinary tract infection (cLUTI) with complicating factors. Specifically, subject had to meet all of the inclusion criteria listed below:

1. Provided written informed consent prior to any study-related procedure not part of normal medical care (a legally acceptable representative provided consent if the subject was unable to do so, provided this was approved by local country and institution specific guidelines).
2. Males or females ≥18 years of age.
3. If female, subject was nonlactating, and was either (a) not of child-bearing potential; or (b) was abstaining from sexual intercourse or using effective birth control.
4. Males were required to practice reliable birth control methods during the conduct of the study and for at least 35 days after the last dose of study medication.
5. Pyuria, defined as 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:
        - Documented fever (oral temperature >38 degrees Celsius) accompanied by subject symptoms of rigors, chills, or warmth;
        - Flank pain;
        - Costovertebral angle tenderness or suprapubic tenderness on physical exam;
        - Nausea or vomiting;

b. Complicated lower UTI, as indicated by at least 2 of the following new or worsening symptoms of cUTI:
    - Dysuria; urinary frequency or urinary urgency;
    - Documented fever (oral temperature >38 degrees Celsius) accompanied by subject symptoms of rigors, chills, or warmth;
    - Suprapubic pain or flank pain;
    - Costovertebral angle tenderness or suprapubic tenderness on physical exam;
    - Nausea or vomiting;

    PLUS, at least 1 of the following complicating factors:
    - Males with documented history of urinary retention;
    - Indwelling urinary catheter that was scheduled to be removed during intravenous study therapy and before the end of antibacterial therapy;
    - Current obstructive uropathy that was scheduled to be medically or surgically relieved during intravenous study therapy and before the end of intravenous therapy;
    - Any functional or anatomical abnormality of the urogentical tract (including anatomic malformations or neurogenic bladder) with voiding disturbance resulting in at least 100 mL residual urine.

7. Had a pre-treatment baseline urine culture specimen obtained within 24 hours before the start of administration of the first dose of the study drug.
8. Required intravenous antibacterial therapy for treatment of the presumed cUTI.

Subjects were excluded from participation if they met any of the following criteria:

1. Had a documented history of any moderate or severe hypersensitivity or allergic reaction to any beta-lactam or quinolone antibacterial drug. For beta-lactams, a history of mild rash followed by uneventful re-exposure was not a contraindication to enrollment.
2. Had a concomitant infection at the time of randomization, which required nonstudy systemic antibacterial therapy in addition to intravenous study drug therapy. Drugs with only Gram-positive activity (e.g., vancomycin, linezolid) were allowed.
3. Receipt of any amount of potentially therapeutic antibacterial therapy after collection of the pre-treatment 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 infection within 48 hours before the study-qualifying pre-treatment baseline urine culture was obtained. Exceptions included subjects receiving current antibiotic prophylaxis for cUTI who presented with signs and symptoms consistent with an active new cUTI.
5. Intractable urinary infection at baseline anticipated to require more than 7 days of study drug therapy.
6. Complete, permanent obstruction of the urinary tract.
7. Confirmed fungal urinary tract infection at the time of randomization.
8. Permanent indwelling bladder catheter or urinary stent including nephrostomy.

9. Suspected or confirmed perinephric or intrarenal abscess.
10. Suspected or confirmed prostatis.
11. Illeal loop or known vesico-ureteral reflux.
12. Severe impairment of renal function including an estimated creatinine clearance <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 (intermittent straight catheterization during the intravenous study drug administration period was acceptable).
14. Any condition or circumstance that, in the opinion of the investigator, compromised the safety of the subject or the quality of the data.
15. Any rapidly progressing disease or immediately life-threatening illness including acute hepatic failure, respiratory failure, or septic shock.
16. Immunocompromising condition, including established AIDS, hematological malignancy, or bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention or 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: aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or total bilirubin level greater than 3 times the upper limit of normal, absolute neutrophil count less than 500/µL, platelet count less than 40,000/ µL or hematocrit less than 20%.
18. Participation in any clinical study of an investigational product within 30 days prior to the proposed first day of study drug.
19. Previous participation in any study of ceftolozane or ceftolozane/tazobactam.
20. Women who were pregnant or nursing.

3.2.1.3 Study drug therapy and control group

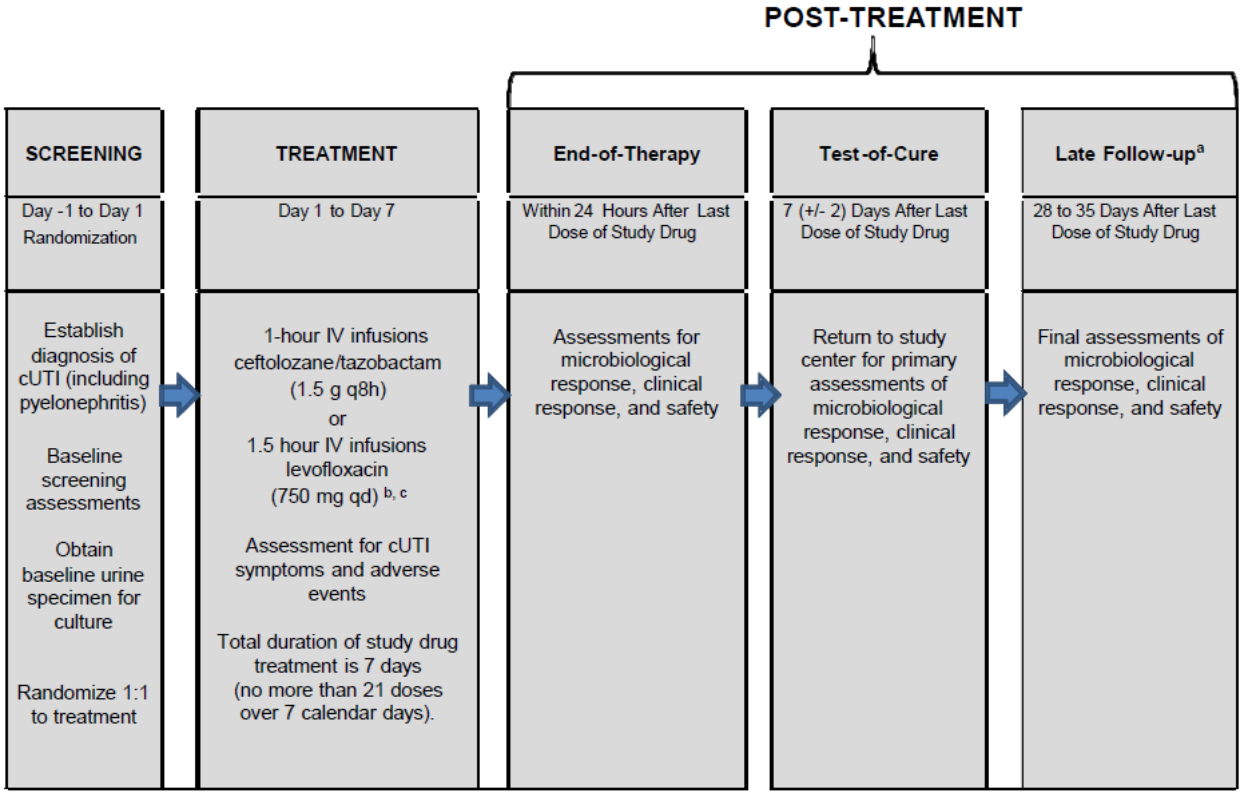
Adult subjects with cUTI were randomized to ceftolozane/tazobactam, administered as an intravenous infusion at a dose of 1.5 g every 8 hours, or to the active control levofloxacin, administered as an intravenous infusion at a dose of 750 mg once daily.

The active control drug, levofloxacin, is an antibacterial drug that is FDA-approved for the treatment of cUTI. It is in the fluoroquinolone class of antibiotics, which operate by inhibiting bacterial DNA synthesis.

3.2.1.4 Visits and procedures

After a baseline visit, subjects were to be treated for up to 7 days with study drug therapy, have an end-of-therapy (EOT) visit within 24 hours of the last dose of study drug, return for a test-of-cure visit 7 (± 2) days after the last dose of study drug, and have (possibly by telephone) a late follow-up (LFU) visit 28-35 days after the last dose of study drug. The following figure and table from the Clinical Study Report illustrate this schedule.

Figure 1: Study Design



[a] The LFU visit was either an in-person evaluation or via telephone contact.

[b] A double-dummy infusion (saline) was used to maintain the blind.

[c] The first dose given each calendar day consisted of 2 infusions given simultaneously: 1 active infusion, 1 dummy infusion. There were 4 daily infusions (3 doses) for subjects in each randomized group.

Source: Clinical Study Report, Figure 1.

Table 2: Schedule of assessments

Study Procedure	Study Visit	Screening (Days -1 to 1)		Treatment (Days 1 to 7)			Follow-up Visits (post last dose)		
	Assessment	Day -1	Day 1[a]	Day 2[b]	Day 3[b]	Days 4-7[b]	EOT ≤24 hours	TOC[c] 7 (±2) days	LFU[c,d] 28-35 days
Baseline	Informed consent	X							
	Inclusion/Exclusion Criteria	X							
	Medical/surgical history	X							
	Randomization		X						
Central Laboratory	Blood sample[e]	X			X		X	X	X[f]
	Urinalysis and urine microscopy	X			X		X	X	X[f]
Local Laboratory	Urine microscopy for pyuria	X							
	Serum pregnancy test	X						X	
	Blood sample [g]	X		X[f]	X	X[f]			
	Urine culture	X			X	X[f]	X[f]	X	X[f]
	Blood culture	X[f]		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]

Study Procedure	Study Visit	Screening (Days -1 to 1)		Treatment (Days 1 to 7)			Follow-up Visits (post last dose)		
	Assessment	Day -1	Day 1[a]	Day 2[b]	Day 3[b]	Days 4-7[b]	EOT ≤24 hours	TOC[c] 7 (±2) days	LFU[c,d] 28-35 days
Clinical	Vital signs[h]	X	X	X	X	X	X	X	
	Complete physical exam	X							
	Targeted physical exam						X	X	
	Height and weight	X							
	Prior and/or concomitant medications	X	X	X	X	X	X	X	X
	Symptom assessment	X	X	X	X	X	X	X[i]	X[f]
	Adverse events		X	X	X	X	X	X	X
	Clinical outcome						X	X	X[f]
	IV infusion[j]		X	X	X	X			

EOT = End-of-therapy visit; TOC = Test-of-cure visit; LFU = Late follow-up visit.
[a] On Day 1, all study procedures, except adverse event collection, were performed prior to IV infusion.
[b] For Study Days 2 through 7 all study assessments were performed at a consistent time of day for the study subject (eg, every morning) for each calendar day.
[c] For TOC and LFU, days indicated were the number of days after administration of the last dose of study drug.
[d] It was permissible to conduct the LFU visit by telephone.
[e] Blood sampling for coagulation, hematology, and chemistry evaluations. Local results were used for baseline qualification.
[f] When clinically indicated.
[g] Blood sampling for creatinine and estimate of creatinine clearance.
[h] Including pulse rate (beats per minute [bpm]), systolic and diastolic blood pressure (BP; mmHg), and oral temperature (°C).
[i] Patient Symptom Questionnaire completed. The Patient Symptom Questionnaire collection and description were modified in protocol amendment 1.1 (prior to first subject enrollment). See Section 9.8.1 for further details. A copy of the Patient Symptom Questionnaire is provided in the case report form in Appendix 16.1.2.
[j] Ceftolozane/tazobactam IV infusion (1.5 g every 8 hours) or levofloxacin IV infusion (750 mg once daily).

Source: Clinical Study Report, Table 5.

In this trial, there was no differentiation between an end-of-therapy visit and an end-of-intravenous-therapy visit because the protocol did not include provisions for switching to oral treatment. Subjects were planned for hospitalization during the entire duration of the planned 7 days of therapy. Subjects undergoing urinary procedures during the treatment period, including removal of an indwelling catheter, could receive up to 9 days of study drug. Due to the timing of visit windows, subject participation required a minimum commitment of 35 days and a maximum commitment of 42 days.

3.2.1.5 Withdrawal from study assessments and withdrawal from study therapy

The Applicant's protocol differentiated between withdrawal from the study drug and withdrawal from study assessments. Reasons for withdrawal from the study included withdrawal of consent, significant subject noncompliance with study assessments, or investigator determination that withdrawal was in the subject's best interest for reasons other than safety or insufficient therapeutic effect. Only 16/800 (2.0%) subjects in the primary efficacy analysis population withdrew from the trial.

As noted, treatment for cUTI is initiated before microbiological culture results are available within 48-72 hours that identify the causative pathogen needed for a proper diagnosis, and the pathogen's susceptibility to different antibacterial therapies. Hence, subjects could be enrolled and given study drug before culture results were available from a specimen taken at baseline. If the culture results were found to be negative for a bacterial pathogen or could not be performed, subjects were to discontinue investigational therapy. However, these subjects were to remain in the trial for safety assessments.

Subjects could also be discontinued from study drug for other reasons including adverse events, lack of efficacy, or protocol violations. Subjects who discontinued therapy early were to undergo the EOT visit on the day of discontinuation. If a subject did not have a qualifying baseline urine culture or was considered a "clinical failure" on the day of premature discontinuation, the protocol specified that he or she did not need to have a TOC or LFU visit.

3.2.1.6 Blinding

As mentioned above, this trial was double-blinded. Because ceftolozane/tazobactam was given three times daily and levofloxacin was given once daily, the blind was maintained through a double dummy design using saline infusions. The Applicant states that with the exception of unblinded study site pharmacists or designees, the subject and all study staff who evaluated the subject and made decisions about the subject's care were blinded to the study drug assignment, and likewise that the site personnel and Applicant itself were blinded to the study drug codes while monitoring and conducting the trial. The protocol specified that unblinding could be performed in the case of a medical emergency requiring the investigator to know the identity of the intravenous therapy being administered. However, this did not occur. There were 7/800 (<1%) subjects in the primary efficacy analysis population for whom suspected accidental unblinding was reported during the trial (Clinical Study Report, Section 10.2). This number was sufficiently small that this reviewer did not consider this trial to be affected by possible open label biases.

3.2.1.7 Prior and concomitant therapy

As described in the inclusion and exclusion criteria, with limited exceptions the protocol disallowed potentially effective antibiotic therapy within 48 hours prior to obtaining the baseline culture. In the primary efficacy analysis population, the rates of prior antibiotic therapy were 19/398 (4.8%) in the ceftolozane/tazobactam group and 13/402 (3.2%) in the levofloxacin group (Clinical Study Report, Table 14.1.7.1.1). The protocol specified that the study drug in each group was to be given as monotherapy. In the primary efficacy analysis population, rates of concomitant nonstudy antibiotics were 17/398 (4.3%) in the ceftolozane/tazobactam group and 17/402 (4.2%) in the levofloxacin group (Clinical Study Report, Table 14.2.32.1). Overall, this reviewer considered prior and concomitant therapy to be relatively limited and roughly evenly distributed between the two groups.

3.2.1.8 Analysis populations

The protocol and statistical analysis plans specified the following analysis populations:

- Intent-to-treat (ITT): All randomized subjects.
- Modified Intent-to-Treat (MITT): All randomized subjects who received any amount of study drug.

- Modified Microbiological Intent-to-Treat (mMITT): The subset of the MITT population that included subjects who had at least 1 qualified uropathogen from a study-qualifying pre-treatment baseline urine specimen.
- Clinically Evaluable at Test-of-Cure (CE at TOC): The subset of the mMITT population who sufficiently adhered to study procedures and had a TOC visit within the specified visit window.
- Microbiologically Evaluable at Test-of-Cure: The subset of the CE at TOC population who had an appropriately collected baseline urine culture specimen and interpretable urine culture result at the TOC visit.
- Safety population: All subjects who received any amount of the study drug. Subjects in this population were categorized based on the actual treatment received, irrespective of the treatment to which they were randomized.

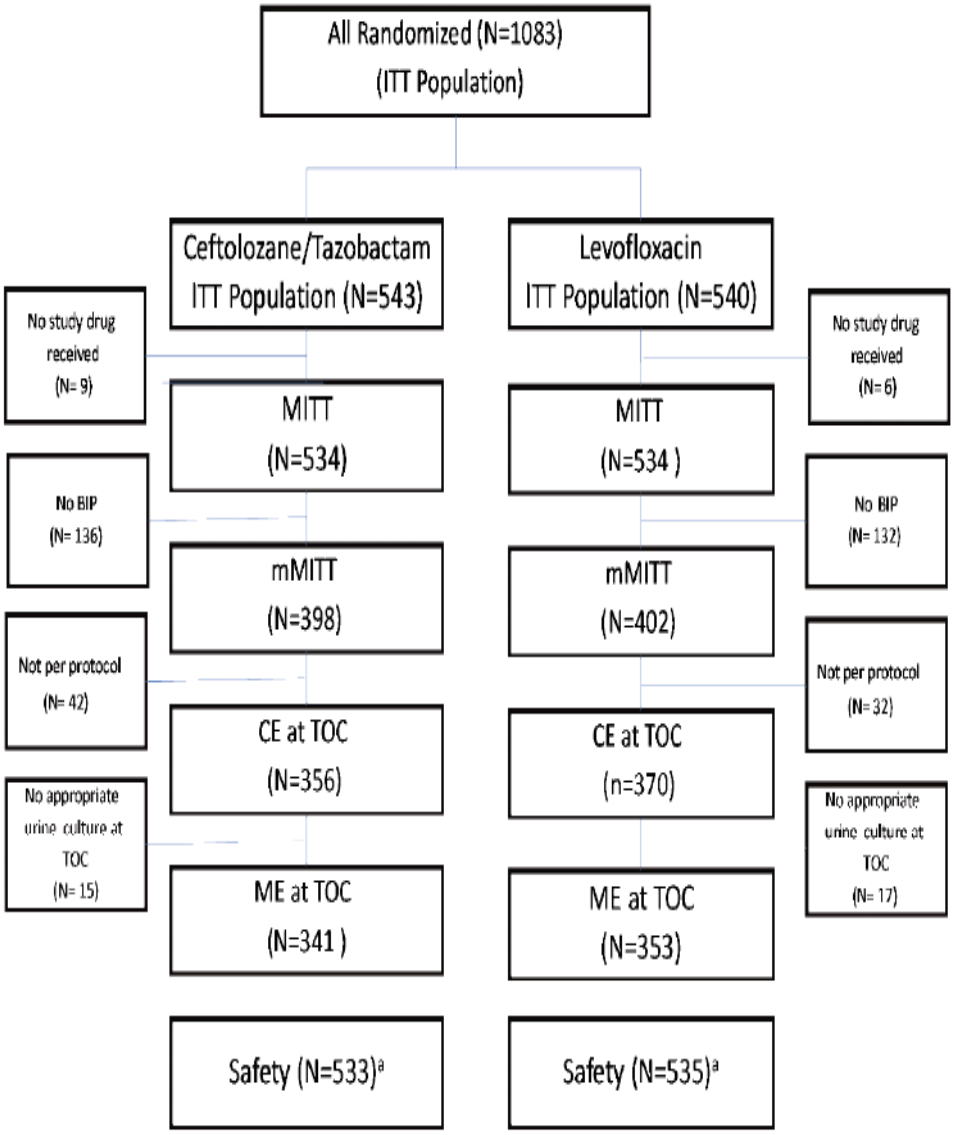
The primary efficacy analysis population was the mMITT population, while the primary safety analysis population was the Safety population.

For defining a study-qualifying pre-treatment baseline urine culture specimen, the specimen must have been obtained within 36 hours before the start of administration of the first dose of study drug and at least 48 hours after the last dose of a potentially therapeutic antibacterial therapy administered for the current cUTI. Urine specimens for culture must have been obtained by either an adequate midstream clean catch, by urethral catheterization, or by suprapubic aspiration. Specimens from Foley bags were not allowed. If more than 1 appropriately collected urine culture specimen was obtained before initiating study drug therapy, the specimen collected at the closest time to the first dose of study drug was considered the baseline specimen. A baseline uropathogen was considered qualifying for the study if it was obtained from a study qualifying pretreatment urine culture growing at $\geq 10^5$ CFU/mL.

The following organisms were considered causative pathogens for cUTI: *ACINETOBACTER BAUMANNII, ACINETOBACTER SPP., BURKHOLDERIA CEPACIA, CITROBACTER FREUNDII, CITROBACTER SPP., ENTEROBACTER AEROGENES, ENTEROBACTER CLOACAE, ENTEROBACTER SPP., ENTEROCOCCUS FAECALIS, ENTEROCOCCUS FAECIUM, ESCHERICHIA COLI, GARDNERELLA VAGINALIS, KLEBSIELLA OXYTOCA, KLEBSIELLA SPP., KLEBSIELLA PNEUMONIAE, MORAXELLA CATTARRHALIS, MORGANELLA MORGANII, PROTEUS MIRABILIS, PSEUDOMONAS AERUGINOSA, SERRATIA SPP., SERRATIA MARCESCENS, STAPHYLOCOCCUS AUREUS, PROVIDENCIA SPP*.

The figure below displays the number of subjects in various analysis populations, in addition to the reasons why subjects were excluded from different populations.

Figure 2: Analysis populations



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

Source: Clinical Study Report, Figure 2.

This reviewer considered the mMITT population to be appropriate for the primary efficacy analysis. Although this was a subgroup of the overall ITT population comprised of all randomized subjects, this reviewer considered it a proper baseline subgroup that was protected from confounding by randomization, allowing unbiased estimation of causal effects. While the mMITT population was defined by culture results that were not available to investigators until after randomization, it was considered a baseline subgroup because the specimens were taken before randomization. In addition, as few randomized subjects were excluded due to not receiving either study drug [15/1083 (1.4%)] and the trial was double-blind, this reviewer did not consider the exclusion of ITT subjects from the MITT population a significant source of bias.

Conversely, the Clinically Evaluable and Microbiologically Evaluable populations were not necessarily protected from confounding by randomization because they were defined in part by post-baseline events such as compliance and other exclusion factors. Thus, this review focuses on the mMITT population used for the primary efficacy analysis.

3.2.1.9 Study endpoints

The primary efficacy endpoint was the composite outcome in which success for a subject was defined by both clinical cure and microbiological eradication at the TOC visit. The corresponding definitions for clinical and microbiological responses at both the EOT and TOC visits are defined in the table below. As noted, the primary analysis was conducted in the mMITT population.

The pre-specified secondary efficacy endpoints included the same composite clinical and microbiological endpoint in the ME population at the TOC visit, clinical response at the EOT, TOC, and LFU visits, microbiological responses at the EOT, TOC, and LFU visits, and per-pathogen microbiological eradication rates.

The primary endpoint was consistent with the aforementioned draft guidance. However, the thinking of this reviewer is that treatment effects on the clinical and microbiological components of the composite can potentially leave several questions unanswered. First, a treatment effect on the microbiological endpoint may not reflect patient benefit in terms of feeling, function, or survival, which is the ultimate measure of efficacy.[2] If the only advantage of a drug is to reduce rates of asymptomatic bacteriuria, which is common and often does not require treatment,[3] it is unclear why the drug should be considered more effective than its comparator. The clinical cure endpoint is potentially affected by similar limitations, to the extent that it is influenced by microbiological results, use of rescue therapy (which in and of itself is not a measure of patient detriment), clinical signs, or other biomarkers.

Second, this reviewer's view is that the clinical cure endpoint is not sufficiently well-defined, and the meaningfulness of the endpoint cannot be assured if it is unclear what the endpoint measures. According to the Code of Federal Regulations[4], one criterion for a clinical investigation to be adequate and well-controlled is that "The methods of assessment of subjects' responses are well-defined and reliable," meaning "The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response." This reviewer does not consider the overall judgment of resolution within the Applicant's cure endpoint to meet this criterion.

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[2] United States versus Rutherford, 1979. This Supreme Court majority decision interpreting the Food, Drug, and Cosmetic Act states that "a drug is effective if it fulfills, by objective indices, its sponsor's claims of prolonged life, improved physical condition, or reduced pain."
[3] Lindsay N.E. et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clinical Infectious Diseases*, 2005;40:643-654.
[4] 21CFR314.126(b).

Table 3: Study endpoints

Endpoint	Outcome category	Definition
Composite of microbiological success and clinical response	Cure	Microbiological response was success and the clinical response was cure.
	Failure	Microbiological response was failure or the clinical response was failure.
	Indeterminate	Microbiological response was indeterminate and the clinical response was indeterminate.
Clinical response at the EOT or TOC visit	Clinical cure	Complete resolution of, marked improvement in (where improvement was defined as reduction in severity of all baseline signs and symptoms with worsening of none and with no requirement for additional antibiotic therapy after EOT), or return to pre-infection signs and symptoms and no use of additional or nonstudy antimicrobial therapy for the treatment of the current cUTI.
	Clinical failure	Persistence of 1 or more sign or symptom of infection or reappearance of or new signs and symptoms that requires additional or alternative antimicrobial therapy for the current cUTI OR Adverse event leading to study drug discontinuation and the subject required nonstudy antimicrobial therapy for the current cUTI.
	Indeterminate	Study data were not available for the evaluation of clinical outcome for any reason or the outcome assessment was confounded.
Microbiological response at the EOT or TOC visit	Eradication	A urine culture shows all uropathogens found at baseline at 10^5 CFU/mL reduced to $<10^4$ CFU/mL.
	Persistence	A urine culture grows $\geq 10^4$ CFU/mL.
	Indeterminate	No interpretable urine culture is available. Eradication was presumed at the EOT if the last culture was taken on or after 3 days of study drug administration.

Source: Clinical Study Report, Section 9.5.3.

3.2.1.10 Combination product evaluation

Because the ceftolozane/tazobactam product under review is the combination of both an antibacterial drug (ceftolozane) and a beta-lactamase inhibitor (tazobactam), an ideal program would assess the added contribution of tazobactam through a three-arm trial randomizing subjects to ceftolozane/tazobactam, ceftolozane, or an active control. Note that tazobactam could not ethically be given as monotherapy due to its lack of antibacterial activity. Because this two arm trial only randomized subjects to ceftolozane/tazobactam or to levofloxacin, it was not possible to directly assess whether the *in vitro* properties of tazobactam translated into better clinical outcomes for the combination product relative to ceftolozane alone. However, the Division agreed with the two-arm design before the trial was initiated due to feasibility constraints.

3.2.2 Statistical Methodologies

3.2.2.1 Hypothesis testing and non-inferiority trials

The primary efficacy analysis evaluated the non-inferiority of ceftolozane/tazobactam relative to the active comparator, levofloxacin, in terms of the composite clinical and microbiological endpoint at the TOC visit in the mMITT population.

The non-inferiority margin was 10% on the risk difference scale. The Applicant tested the non-inferiority hypothesis at the one-sided $\alpha = 0.025$ level. This was done by forming a two-sided 95% confidence interval for the difference in success rates between ceftolozane/tazobactam and levofloxacin, and rejecting the hypothesis if the lower confidence limit for the treatment difference exceeded -0.10.

The Applicant's confidence interval for the primary analysis was constructed using the Newcombe method, with the analysis stratified by region. Unless otherwise noted, the confidence intervals reported by this reviewer use the Miettinen-Nurminen method, were not stratified, and did not qualitatively differ from the Applicant's confidence intervals.

For the purpose of the primary analysis, subjects classified as "Indeterminate" according to Table 3 were counted as failures when reporting the estimated treatment effect for the difference in cure rates.

Consistent with this application, the 2012 FDA guidance document discussed in Section 2.1.4 of this review recommended that non-inferiority trials of antibacterial drugs for cUTIs use a non-inferiority margin no larger than 10% on the risk difference scale. Much of that guidance document revolved around justifying the 10% non-inferiority margin and recommending design considerations to enhance assay sensitivity in non-inferiority trials. The objective of a non-inferiority trial is to evaluate whether or not a new intervention is unacceptably worse than an existing regimen. Note that the win criterion with a 10% margin requires ruling out with statistical confidence that the new therapy is no more than 10% worse than the control in terms of success rates for the primary endpoint.

There are many well-known complications of non-inferiority trials. For instance, showing similarity to the control would only provide evidence of efficacy if one can argue from external data that the control is itself effective. Likewise, showing similarity between groups would have an unclear interpretation if the non-inferiority trial was not sensitive to detect differences, such as if subjects in both arms also received effective prior or concomitant therapy, or if it was unclear whether subjects were properly diagnosed with the disease. Non-inferiority trials are generally less directly interpretable than superiority trials, meaning studies that evaluate whether a new intervention leads to better results than the control, because these aforementioned factors tend to drive results toward the win criterion rather than away from it.

However, the limitations of non-inferiority trials did not affect the primary efficacy analysis in this application. As will be discussed, although this Phase 3 cUTI trial was

designed as a non-inferiority study, ceftolozane/tazobactam met criteria for achieving statistical superiority relative to the active control.

3.2.2.2 Randomization and sample size

Subjects were randomized in a 1:1 ratio to either ceftolozane/tazobactam or to levofloxacin, with the randomization stratified by investigational site. The Applicant's final statistical analysis plan made the following comments regarding sample sizes: "*The final sample size of the study will be 954 subjects (477 per arm), achieved by pooling the subjects enrolled in both the CXA-cUTI-10-04 and CXA-cUTI-10-05 protocols. Similar numbers of subjects are expected from each protocol. Subjects will be randomized 1:1 to receive ceftolozane/tazobactam or comparator (IV levofloxacin) resulting in an estimated 405 mMITT subjects per treatment arm. A sample size of 954 will ensure a minimum of 90% power to demonstrate non-inferiority of ceftolozane/tazobactam to IV levofloxacin at a 10% NI margin and one-sided significance level of 0.025 in the mMITT population. These calculations assume 85% of randomized subjects would meet the criteria to be included in the mMITT population and that the cure rate (composite microbiological response and clinical response rate at the TOC visit in the mMITT population) in both arms would be 74%.* However, although 954 subjects were planned for the trial, Section 10.1 of the Applicant's Clinical Study Report states that "*A total of 1083 subjects were randomized into the study to achieve the target mMITT evaluable sample size of approximately 800 subjects*." The final mMITT sample sizes were 398 subjects in the ceftolozane/tazobactam group and 402 subjects in the levofloxacin group, in line with the Applicant's originally estimated 405 subjects per arm.

Because the mMITT population was used for the primary analysis, and accordingly should have driven the power calculations, this reviewer does not see potential bias from discrepancies between the actual sample size and statistical analysis plan, provided that no sample size adjustments were made prior to unblinding data to treatment assignments.

This trial did not have a data monitoring committee, and no interim analyses or corresponding sample size modifications were performed.

3.2.2.3 Pooling

As discussed in Section 2.1.5 of this review, CXA-cUTI-10-04 and CXA-cUTI-10-05 were pooled into a single trial while these studies were ongoing and the Applicant was blinded to results. Supportive evidence for safety and efficacy will come from a separate cIAI trial rather than a fully powered replicated trial in subjects with cUTI. Except where otherwise noted, analyses in both the Applicant's Clinical Study Report and within this review are based on the pooled data pre-specified for the primary analysis. Given that there is no inflation of Type I error from pooling analysis sets prior to unblinding of data, and that the pooled studies had identical protocols and were conducted in overlapping regions, this reviewer considered the Applicant's pooled analysis strategy to be statistically appropriate.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The following tables describe the demographics and baseline characteristics of subjects in the mMITT population used for the primary efficacy analysis. Recall that this population was comprised of randomized subjects who received any amount of study drug and had a baseline infecting pathogen, and that the reasons for exclusion from the mMITT were previously described in Figure 2.

Table 4: Demographic and baseline characteristics (mMITT population)

Characteristic	Ceftolozane/ Tazobactam (N=398)	Levofloxacin (N=402)	Total (N=800)
Age (years)	n=398	n=402	n=800
Mean (Standard deviation)	49.1 (19.71)	48.1 (20.20)	48.6 (19.95)
Median	51.0	49.5	50.5
Minimum, Maximum	18, 90	18, 87	18, 90
Age Groups 1	n (%)	n (%)	n (%)
≥18 - <65	298 (74.9)	303 (75.4)	601 (75.1)
≥65 - <75	57 (14.3)	53 (13.2)	110 (13.8)
≥75	43 (10.8)	46 (11.4)	89 (11.1)
Age Groups 2[a]	n (%)	n (%)	n (%)
≥18 - <45	165 (41.4)	182 (45.3)	347 (43.4)
≥45 - <65	133 (33.4)	121 (30.1)	254 (31.8)
≥65	100 (25.1)	99 (24.6)	199 (24.9)
Sex	n (%)	n (%)	n (%)
Male	105 (26.4)	103 (25.6)	208 (26.0)
Female	293 (73.6)	299 (74.4)	592 (74.0)
Race	n (%)	n (%)	n (%)
White	340 (85.4)	346 (86.1)	686 (85.8)
Black or African American	6 (1.5)	6 (1.5)	12 (1.5)
Asian	34 (8.5)	33 (8.2)	67 (8.4)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	18 (4.5)	17 (4.2)	35 (4.4)
Not Applicable	0	0	0
Ethnicity	n (%)	n (%)	n (%)
Hispanic or Latino	46 (11.6)	48 (11.9)	94 (11.8)
Not Hispanic or Latino	331 (83.2)	330 (82.1)	661 (82.6)
Not Applicable	21 (5.3)	24 (6.0)	45 (5.6)

Source: Clinical Study Report, Table 16.

Table 5: Other demographic and baseline characteristics (mMITT population)

Characteristic	Ceftolozane/ Tazobactam (N=398)	Levofloxacin (N=402)	Total (N=800)
BMI (kg/m^2)	n=397	n=399	n=796
Mean (Standard deviation)	25.52 (5.76)	26.11 (5.60)	25.81 (5.69)
Median	24.65	25.30	24.90
Minimum, Maximum	15.8, 55.3	15.3, 53.2	15.3, 55.3
Baseline Creatinine Clearance (mL/min)	n=397	n=402	n=799
Mean (Standard deviation)	93.642 (34.98)	98.196 (35.03)	95.933 (35.06)
Median	89.372	96.583	92.631
Minimum, Maximum	21.99, 249.71	21.52, 246.92	21.52, 249.71
Creatinine Clearance at baseline [b]	n (%)	n (%)	n (%)
CL_{CR} ≥80 mL/min (normal)	247 (62.1)	274 (68.2)	521 (65.1)
CL_{CR} >50 - <80 mL/min (mild impairment)	116 (29.1)	100 (24.9)	216 (27.0)
CL_{CR} ≥30 - ≤50 mL/min (moderate impairment)	31 (7.8)	27 (6.7)	58 (7.3)
CL_{CR} <30 mL/min (severe impairment)	3 (0.8)	1 (0.2)	4 (0.5)
Diagnosis	n (%)	n (%)	n (%)
Pyelonephritis	328 (82.4)	328 (81.6)	656 (82.0)
cLUTI	70 (17.6)	74 (18.4)	144 (18.0)

Source: Clinical Study Report, Table 16.

Randomization appeared to have succeeded in balancing the ceftolozane/tazobactam and levofloxacin groups on the displayed baseline variables.

One notable characteristics of the mMITT population were that the majority of patients had pyelonephritis rather than cLUTI.

Demographically, the trial enrolled predominately Whites, females, and subjects without moderate or severe renal impairment. Approximately 25% of patients were age ≥65 years.

The next table shows clinical signs and symptoms in the MITT analysis population, for subjects with pyelonephritis and for subjects with cLUTI. In line with the inclusion criteria requiring signs and symptoms of disease for a proper diagnosis, a large number of subjects had symptoms such as flank pain, costovertebral angle tenderness of suprapubic tenderness, nausea or vomiting, and dysuria, increased urinary frequency, or increased urinary urgency. Clinical signs, symptoms, and abnormalities were roughly evenly balanced between the randomized ceftolozane/tazobactam and levofloxacin groups.

Table 6: Baseline clinical signs and symptoms (mMITT population)

Clinical Signs and Symptoms	Ceftolozane/ Tazobactam (N=398) n (%)	Levofloxacin (N=402) n (%)	Total (N=800) n (%)
Number of subjects with pyelonephritis, N1 (1)	328 (82.4)	328 (81.6)	656 (82.0)
(a) Fever (oral temperature > 38° C) accompanied by symptoms of rigors, chills or warmth (2)	258 (78.7)	267 (81.4)	525 (80.0)
(b) Flank Pain (2)	313 (95.4)	312 (95.1)	625 (95.3)
(c) Costovertebral angle tenderness or suprapubic tenderness on physical exam (2)	298 (90.9)	297 (90.5)	595 (90.7)
(d) Nausea or vomiting (2)	175 (53.4)	171 (52.1)	346 (52.7)
Number of subjects with cLUTI, N2 (1)	70 (17.6)	74 (18.4)	144 (18.0)
(e) Dysuria, frequency, or urinary urgency (3)	64 (91.4)	69 (93.2)	133 (92.4)
(f) Documented fever with rigors, chills or warmth (3)	17 (24.3)	16 (21.6)	33 (22.9)
(g) Suprapubic or flank pain (3)	61 (87.1)	70 (94.6)	131 (91.0)
(h) Costovertebral angle or suprapubic tenderness on physical exam (3)	53 (75.7)	58 (78.4)	111 (77.1)
(i) Nausea or vomiting (3)	19 (27.1)	9 (12.2)	28 (19.4)
Clinical Signs and Symptoms	**Ceftolozane/ Tazobactam (N=398) n (%)**	**Levofloxacin (N=402) n (%)**	**Total (N=800) n (%)**
(j) Males with documented urinary retention (3)	35 (50.0)	28 (37.8)	63 (43.8)
(k) Indwelling catheter to be removed during IV treatment and before EOT	10 (14.3)	6 (8.1)	16 (11.1)
(l) Current obstructive uropathy scheduled to be medically/surgically relieved during IV treatment and before EOT (3)	9 (12.9)	9 (12.2)	18 (12.5)
(m) Functional/anatomical urogenital tract abnormality with voiding disturbance (3)	35 (50.0)	45 (60.8)	80 (55.6)
Number of above (j-m) complicating factors (3) 0	1 (1.4)	0	1 (0.7)
1	52 (74.3)	61 (82.4)	113 (78.5)
≥2	17 (24.3)	13 (17.6)	30 (20.8)

cLUTI = Complicated lower urinary tract infection; EOT = End of therapy; IV = Intravenous; mMITT=Microbiological modified Intent-to-Treat.

Notes: n=Number of subjects in specific category. N=Number of subjects in mMITT population. N1=Number of subjects in mMITT population with pyelonephritis. N2=Number of subjects in mMITT population with cLUTI.

(1) Percentages are calculated as 100 x (n/N), percentage of subjects in mMITT population.

(2) Percentages are calculated as 100 x (n/N1), percentage of subjects in mMITT population with pyelonephritis.

(3) Percentages are calculated as 100 x (n/N2), percentage of subjects in mMITT population with cLUTI.

Source: Clinical Study Report, Table 17.

The next table shows the baseline pathogens in the mMITT population. The most common pathogen was *E. coli*, which infected approximately 80% of patients. Other pathogens were relatively rare. In particular, although ceftolozane/tazobactam was evaluated in part due to its *in vitro* activity against *P. aeruginosa*, only 8 infected patients were randomized to the ceftolozane/tazobactam group.

Table 7: Baseline urine and blood pathogens; mMITT population

Pathogen Group Pathogen Category Pathogen	Ceftolozane/ Tazobactam (N=398) n (%)	Levofloxacin (N=402) n (%)	Total (N=800) n (%)
Baseline Urine Pathogens			
Gram-Negative Aerobes	378 (95.0)	386 (96.0)	764 (95.5)
Enterobacteriaceae	369 (92.7)	370 (92.0)	739 (92.4)
Escherichia coli	305 (76.6)	324 (80.6)	629 (78.6)
Klebsiella pneumoniae	33 (8.3)	25 (6.2)	58 (7.3)
Proteus mirabilis	12 (3.0)	12 (3.0)	24 (3.0)
Enterobacter spp.	10 (2.5)	9 (2.2)	19 (2.4)
Other Enterobacteriaceae	12 (3.0)	7 (1.7)	19 (2.4)
Pseudomonas aeruginosa	8 (2.0)	15 (3.7)	23 (2.9)
Other[a]	2 (0.5)	1 (0.2)	3 (0.4)
Gram-Positive Aerobes	25 (6.3)	23 (5.7)	48 (6.0)
Enterococcus faecalis	20 (5.0)	18 (4.5)	38 (4.8)
Other[a]	6 (1.5)	5 (1.2)	11 (1.4)
Baseline Blood Pathogens			
Number of subjects with bacteremia	29	33	62
Gram-Negative Aerobes	23 (5.8)	27 (6.7)	50 (6.3)
Enterobacteriaceae	22 (5.5)	26 (6.5)	48 (6.0)
Escherichia coli	19 (4.8)	21 (5.2)	40 (5.0)
Other Enterobacteriaceae	4 (1.0)	6 (1.5)	10 (1.3)
Gram-Negative Anaerobes	0	1 (0.2)	1 (0.1)
Gram-Positive Aerobes	6 (1.5)	7 (1.7)	13 (1.6)
Gram-Positive Anaerobes	1 (0.3)	0	1 (0.1)

mMITT=Microbiological modified Intent-to-Treat.

[a] If fewer than 10 subjects reported an isolate overall, the isolate was reported alongside other isolates of the same genus or family which meet the same criteria, and categorized as "Other".

Notes: n=Number of subjects in specific category. N=Number of subjects in mMITT population. Percentages are calculated as 100 x (n/N).

Subjects with more than 1 pathogen isolated at baseline are counted only once in the overall population N, once within each pathogen category and once for each pathogen (n).

If fewer than 10 subjects report an isolate overall, the isolate is reported alongside other isolates of the same genus which meet the same criteria.

Source: Clinical Study Report, Table 18.

The table below shows that the trial was predominately conducted in the Eastern European region. The table displays by order of total enrollment the number of subjects from each country within the two studies, CXA-cUTI-10-04 and CXA-cUTI-10-05, which were pooled to form the single Phase 3 trial. With the exception of Russia and the United States, the two studies were conducted in separate countries.

Of note, only 14/800 (1.8%) subjects in the mMITT population were enrolled from the United States. Whether due to the trial requirements limiting prior antibacterial treatment, the duration of intravenous therapy, or other factors, this potentially limits the generalizability of results to US patients if there are geographic differences in patient management, patient characteristics, clinical trial conduct, or bacterial pathogens.

Table 8: Number of subjects per country in the pooled trials (mMITT population)

Country	CXA-cUTI-10-04 (n = 403)	CXA-cUTI-10-05 (n = 397)	Total mMITT (n = 800)
Ukraine	0/403 (0)	151/397 (38.0)	151/800 (18.9)
Russia	22/403 (5.5)	93/397 (23.4)	115/800 (14.4)
Romania	78/403 (19.4)	0/397 (0)	78/800 (9.8)
Hungary	60/403 (14.9)	0/397 (0)	60/800 (7.5)
Poland	0/403 (0)	57/397 (14.4)	57/800 (7.1)
Georgia	45/403 (11.2)	0/397 (0)	45/800 (5.6)
Colombia	37/403 (9.2)	0/397 (0)	37/800 (4.6)
Latvia	37/403 (9.2)	0/397 (0)	37/800 (4.6)
Thailand	28/403 (6.9)	0/397 (0)	28/800 (3.5)
India	0/403 (0)	25/397 (6.3)	25/800 (3.1)
Peru	0/403 (0)	24/397 (6.0)	24/800 (3.0)
Estonia	20/403 (5)	0/397 (0)	20/800 (2.5)
Israel	20/403 (5.0)	0/397 (0)	20/800 (2.5)
United States	9/403 (2.2)	5/397 (1.3)	14/800 (1.8)
Bulgaria	0/403 (0)	13/397 (3.3)	13/800 (1.6)
South Korea	0/403 (0)	12/397 (3.0)	12/800 (1.5)
Croatia	0/403 (0)	11/397 (2.8)	11/800 (1.4)
Mexico	11/403 (2.7)	0/397 (0)	11/800 (1.4)
Brazil	10/403 (2.5)	0/397 (0)	10/800 (1.3)
Moldova	10/403 (2.5)	0/397 (0)	10/800 (1.3)
South Africa	10/403 (2.5)	0/397 (0)	10/800 (1.3)
Slovenia	0/403 (0)	5/397 (1.3)	5/800 (0.6)
Serbia	4/403 (1.0)	0/397 (0)	4/800 (0.5)
Slovakia	2/403 (0.5)	0/397 (0)	2/800 (0.3)
Chile	0/403 (0)	1/397 (0.3)	1/800 (0.1)

Source: The variable "COUNTRY" in the adsl.xpt ADaM dataset contains the country of each subject. The prefix of subject identifier variable "USUBJID" in this same dataset identifies whether the subject was enrolled in CXA-cUTI-10-04 or CXA-cUTI-10-05.

The following table shows the number of subjects in each treatment group who either withdrew from evaluation or withdrew from study therapy. The protocol appropriately differentiated these two types of withdrawal. In general, to allow unbiased estimation of causal effects an intention-to-treat analysis of a randomized clinical trial requires following subjects for outcome evaluation even if they discontinue therapy. Such an intention-to-treat analysis (or in this trial, mMITT analysis) then estimates the effect of assigning subjects to a treatment group, which is arguably the most important question the trial can answer given that virtually all regimens are associated with some degree of noncompliance.

Only 16/800 (2.0%) subjects in the mMITT population withdrew from evaluation. Thus, this form of loss to follow-up was not a major limitation hindering the trial interpretation.

Discontinuation from study therapy occurred for 55/800 (6.9%) mMITT subjects. The rate of premature discontinuation from therapy was numerically higher in the levofloxacin group than in the ceftolozane/tazobactam group by an amount that was borderline non-significant (p = 0.08, two-sided). The most common reason for study drug discontinuation within each treatment group was withdrawal by the subject, rather than being directly linked to adverse events, lack of efficacy, a protocol violation, a negative or contaminated urine culture, or other factors.

Table 9: Withdrawals from the trial and from therapy (mMITT population)

	Ceftolozane/tazobactam (n = 398)	Levofloxacin (n = 402)
Premature discontinuation from the trial	9/398 (2.3)	7/402 (1.7)
Withdrawal by subject	7/398 (1.8)	3/402 (0.7)
Lost to follow-up	1/398 (0.3)	4/402 (1.0)
Other	1/398 (0.3)	0/402 (0)
Premature discontinuation from study drug	21/398 (5.3)	34/402 (8.5)
Withdrawal by subject	9/398 (2.3)	14/402 (3.5)
Adverse event	6/398 (1.5)	7/402 (1.7)
Lack of efficacy	3/398 (0.8)	5/402 (1.2)
Protocol violation	1/398 (0.3)	1/402 (0.2)
Negative/contaminated urine culture	1/398 (0.3)	0/402 (0)
Other	1/398 (0.3)	7/402 (1.7)

Source: The status for each subject regarding withdrawal from the trial, reason for withdrawal, discontinuation from therapy, and reason for discontinuation were found from the variables “WDFL,” “WDREAS,” “SDFL,” and “SDREAS” in the adsl.xpt ADaM dataset.

Overall, the conclusion of this reviewer was that the patient disposition, balance between treatment groups on baseline variables, and degree of follow-up were acceptable for successfully interpreting a cUTI trial. As previously noted, the main demographic limitation was the few number of subjects enrolled in the United States.

3.2.4 Results and Conclusions

3.2.4.1 Primary efficacy analysis

The table below displays results for the primary efficacy endpoint: the composite clinical and microbiological outcome at the TOC visit in the mMITT population.

Table 10: Primary efficacy endpoint (mMITT population)

Endpoint	Ceftolozane/tazobactam (n = 398)	Levofloxacin (n = 402)	Difference (95% CI)
Composite (TOC)			
Cure	306/398 (76.9)	275/402 (68.4)	8.5 (2.3 to 14.6)
Failure	66/398 (16.6)	103/402 (25.6)	
Indeterminate	26/398 (6.5)	24/402 (6.0)	

Source: Clinical Study Report, Table 20.

Although this trial was designed to evaluate whether ceftolozane/tazobactam was non-inferior to levofloxacin, the above results show that the drug met criteria for demonstrating statistical superiority with respect to the primary endpoint. Specifically, the lower bound of the 95% confidence interval for the treatment difference between the two groups not only exceeded -0.10, as needed for non-inferiority, but exceeded zero.

As discussed in Section 3.2.2.1 of this review, a superiority finding generally provides more directly interpretable evidence of efficacy than a non-inferiority finding because it bypasses several drawbacks inherent in non-inferiority trials. These include the required assumption of a large active control effect relative to a hypothetical placebo arm, the assumed constancy of conditions between the trial under review and historical data used to derive the non-inferiority margin, and noncompliance or irregularities that may bias results in the direction of similarity between treatment groups. Therefore, the superiority finding in this trial provides relatively strong statistical evidence for a treatment effect of ceftolozane/tazobactam on the primary efficacy endpoint.

3.2.4.2 Clinical and microbiological results

The secondary efficacy endpoints included the clinical and microbiological components of the primary composite endpoint. Table 11 below shows that ceftolozane/tazobactam was statistically superior to levofloxacin with respect to rates of microbiological eradication at both the TOC and EOT visits.

The difference in clinical cure rates between the two groups did not meet the criteria for nominal statistical significance at the EOT, TOC, or LFU visit. However, the lower confidence limit for the difference in rates between ceftolozane/tazobactam and levofloxacin did not fall below -0.02 at any of these study visits, although the LFU results were limited by incomplete data. Therefore, the results provide statistical evidence that clinical cure rates under ceftolozane/tazobactam are not markedly worse than those achieved by levofloxacin, under the conditions of this trial.

Table 11: Clinical and microbiological secondary endpoints (mMITT population)

Endpoint	Ceftolozane/tazobactam (n = 398)	Levofloxacin (n = 402)	Difference (95% CI)
Clinical (EOT)			
Cure	375/398 (94.2)	371/402 (92.3)	1.9 (-1.6 to 5.5)
Failure	13/398 (3.3)	21/402 (5.2)	
Indeterminate	10/398 (2.5)	10/402 (2.5)	
Clinical (TOC)			
Cure	366/398 (92.0)	356/402 (88.6)	3.4 (-0.7 to 7.6)
Failure	20/398 (5.0)	35/402 (8.7)	
Indeterminate	12/398 (3.0)	11/402 (2.7)	
Clinical (LFU)			
Sustained cure	348/398 (87.4)	337/402 (83.8)	3.6 (-1.3 to 8.5)
Relapse	14/398 (3.5)	15/402 (3.7)	
Indeterminate	4/398 (1.0)	4/402 (1.0)	
Not applicable	32/398 (8.0)	46/402 (11.4)	
Microbiological (EOT)			
Success	379/398 (95.2)	340/402 (84.6)	10.6 (6.6 to 14.9)
Failure	9/398 (2.3)	46/402 (11.4)	
Non-evaluable	10/398 (2.5)	16/402 (4.0)	
Microbiological (TOC)			
Success	320/398 (80.4)	290/402 (72.1)	8.3 (2.4 to 14.1)
Failure	51/398 (12.8)	85/402 (21.1)	
Non-evaluable	27/398 (6.8)	27/402 (6.7)	
Microbiological (LFU)			
Sustained eradication	53/398 (13.3)	49/402 (12.2)	1.1 (-3.5 to 5.8)
Recurrence	18/398 (4.5)	11/402 (2.7)	
Indeterminate	250/398 (62.8)	236/402 (58.7)	
Not applicable	77/398 (19.3)	106/402 (26.4)	

Source: Clinical Study Report, Tables 22-27.

3.2.4.3 Levofloxacin resistance

Because superiority findings are unusual in non-inferiority trials of antibacterial drugs, this subsection will examine the most likely explanation identified by this reviewer.

The following table from the Applicant's Clinical Study Report shows that despite the fact that this trial used levofloxacin as the active comparator, many baseline pathogens were in fact resistant to levofloxacin. Susceptibility to levofloxacin was based on the definitions of the Clinical and Laboratory Standards Institute[5].

[5] Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement M100: M100-S22, Volume 32, No 3, January 2012.

Table 12: Susceptibility characteristics of baseline pathogens (mMITT population)

	All Subjects (N=800)							
	Ceftolozane/Tazobactam				Levofloxacin			
Pathogen Category Pathogen	N1	S n/N2 (%)	I n/N2 (%)	R n/N2 (%)	N1	S n/N2 (%)	I n/N2 (%)	R n/N2 (%)
Gram-Negative Aerobes	775	706/731 (96.6)	5/731 (0.7)	20/731 (2.7)	775	517/731 (70.7)	19/731 (2.6)	195/731 (26.7)
Enterobacteriaceae	749	694/709 (97.9)	4/709 (0.6)	11/709 (1.6)	749	509/709 (71.8)	18/709 (2.5)	182/709 (25.7)
Escherichia coli	629	592/594 (99.7)	0/594	2/594 (0.3)	629	440/594 (74.1)	10/594 (1.7)	144/594 (24.2)
Klebsiella pneumonia	58	48/55 (87.3)	1/55 (1.8)	6/55 (10.9)	58	26/ 55 (47.3)	5/55 (9.1)	24/ 55 (43.6)
Proteus mirabilis	24	23/23 (100)	0/23	0/23	24	19/ 23 (82.6)	2/23 (8.7)	2/23 (8.7)
Enterobacter spp.	19	15/19 (78.9)	2/ 9 (10.5)	2/19 (10.5)	19	10/ 19 (52.6)	1/19 (5.3)	8/19 (42.1)
Other Enterobacteriaceae	19	16/18 (88.9)	1/18 (5.6)	1/18 (5.6)	19	14/ 18 (77.8)	0/18	4/18 (22.2)
Pseudomonas aeruginosa	23	12/20 (60.0)	1/20 (5.0)	7/20 (35.0)	23	7/ 20 (35.0)	1/20 (5.0)	12/20 (60.0)
Other	3	0/2	0/2	2/2 (100)	3	1/2 (50.0)	0/2	1/2 (50.0)
Gram-Positive Aerobes	49	0/45	0/45	45/45 (100)	49	20/45 (44.4)	2/45 (4.4)	23/45 (51.1)
Enterococcus faecalis	38	0/35	0/35	35/35 (100)	38	15/35 (42.9)	1/35 (2.9)	19/35 (54.3)
Other	11	0/10	0/10	10/10 (100)	11	5/10 (50.0)	1/10 (10.0)	4/10 (40.0)

CLSI = Clinical and Laboratory Standards Institute; mMITT=Microbiological modified Intent-to-Treat; S = Susceptible, I = Intermediate, R = Resistant.
Notes: N=Number of Subjects in mMITT population. N1 = Number of baseline pathogens. N2 = Number of pathogens with a baseline MIC available. n=Number of pathogens within a specific category. Percentages are calculated as 100 x (n/N2).
If fewer than 10 subjects reported an isolate overall, the isolate was reported alongside other isolates of the same genus or family which meet the same criteria.

Source: Clinical Study Report, Table 19.

The enrollment of subjects with baseline pathogens resistant to levofloxacin likely facilitated the superiority demonstration. However, for ethical reasons non-inferiority designs of antibacterial drugs have not traditionally led to a large proportion of subjects resistant to the comparator. Hence, it is important to understand the circumstances of this trial. The final protocol included the following statements regarding resistant pathogens:

- "*If an organism found to be resistant to 1 or both study drugs is isolated from the urine, the Investigator will determine whether the subject should remain on study drug therapy. The determination to discontinue study drug therapy should be based upon the subject's clinical response and not solely on the in vitro susceptibility results. Since in vitro resistance is not always clinically relevant in UTI, the Investigator may decide to continue a subject's study drug treatment if, in the Investigator's opinion, there is clear and continuing clinical improvement while on therapy. Conversely, the Investigator may decide to prematurely discontinue study drug treatment of a subject and to initiate an alternative and appropriate therapy if, in the Investigator's opinion, the subject is not benefiting from therapy.*"
- "*Subjects whose baseline bacterial uropathogen has MICs indicating resistance to either or both study drugs but who are responding well to study drug therapy may continue with the assigned study drug therapy for the entire 7-day (no more than 21 doses over 7 calendar days) study drug treatment period.*"

Thus, the protocol did not require investigators to discontinue subjects with potentially resistant infections from study therapy. As understood by this reviewer, the rationale was that both study drugs achieve high concentrations in the urine, and therefore that the established breakpoints may not be fully informative for guiding cUTI therapy.

The informed consent form for this trial did not discuss potential levofloxacin resistance, or whether the trial hypothesis corresponded to evaluating superiority or non-inferiority, but rather stated that "*The purpose of this study is to learn if the investigational drug CXA-201 (a combination drug that is made up of CXA-101 and tazobactam) can safely and effectively treat cUTI and pyelonephritis, compared to levofloxacin, an approved antibiotic for treatment of cUTI.*" The informed consent section titled "Risks Associated with levofloxacin" discussed several adverse reactions, but did not discuss resistance.

For the ceftolozane/tazobactam group, provisional breakpoints for defining a pathogen as susceptible, intermediate, or resistant in the table were minimum inhibitory concentration ≤8 mg/L, 16 mg/L, and ≥32 mg/L. By these criteria, virtually all *E. coli* isolates were considered susceptible, but only 12/20 (60.0%) *P. aeruginosa* isolates were susceptible.

Resistance to ceftolozane/tazobactam was found in subjects with Gram-positive aerobes. However, this resistance is associated with the general cephalosporin class of antibiotics, of which ceftolozane/tazobactam is a member.

Table 13 below shows that the group of subjects with baseline pathogens resistant to levofloxacin differed from the group without levofloxacin resistance in terms of many baseline characteristics and co-morbidities. Differences reached the level of statistical significance for several demographic factors, subtypes of disease, complicating factors, and infecting pathogens. Therefore, comparisons within a treatment group of outcomes between subjects with and without levofloxacin resistance are likely to be confounded. Because resistance was not randomized, it would be inappropriate to draw conclusions regarding treatment effects or the clinical impact of drug resistance through comparing outcomes between subjects who were and were not infected by resistant pathogens.

Table 14 presents results for clinical and microbiological outcomes in the subset of the mMITT primary analysis population with baseline levofloxacin resistance. Within this subset, there was clearly statistical evidence of large ceftolozane/tazobactam treatment effect relative to levofloxacin on both clinical and microbiological endpoints. Conversely, Table 15 shows results for the subset of the mMITT without levofloxacin resistance, in which one would expect the comparator to be effective. In this subgroup there were no strong trends favoring the superiority of ceftolozane/tazobactam for either clinical or microbiological outcomes, but nominal confidence limits did rule loss of efficacy greater than 10% for all cases considered. Statistically significant interactions showed a greater treatment effect for ceftolozane/tazobactam in the levofloxacin resistant subgroup than in the levofloxacin non-resistant subgroup for the composite endpoint ($p = 0.02$, two-sided), the TOC clinical cure endpoint ($p = 0.01$, two-sided), and the TOC microbiological endpoint ($p = 0.03$, two-sided).

Table 13: Reviewer's analysis of baseline characteristics of subjects with and without a levofloxacin resistant infecting pathogen at baseline (mMITT population)

Baseline characteristics	No levofloxacin resistance (n = 588)	Levofloxacin resistance (n = 212)
Sex		
Male*	118/588 (20.1)	90/212 (42.5)
Female*	470/588 (79.9)	122/212 (57.5)
Age (years)		
18-64*	460/588 (78.2)	141/212 (66.5)
65-74*	71/588 (12.1)	39/212 (18.4)
≥75*	57/588 (9.7)	32/212 (15.1)
Race		
White*	513/588 (87.2)	173/212 (81.6)
Black	9/588 (1.5)	3/212 (1.4)
Asian	48/588 (8.2)	19/212 (9.0)
Region		
North America	17/588 (2.9)	8/212 (3.8)
Eastern Europe	456/588 (77.6)	152/212 (71.7)
South America*	44/588 (7.5)	28/212 (13.2)
Rest of World	71/588 (12.1)	24/212 (11.3)
Disease type		
Pyelonephritis*	508/588 (86.4)	148/212 (69.8)
cLUTI*	80/588 (13.6)	64/212 (30.2)
Body mass index (kg/m^2)		
<25*	333/588 (56.6)	74/212 (34.9)
25-30*	130/588 (22.1)	89/212 (42.0)
>30	122/588 (20.7)	48/212 (22.6)
Creatinine clearance (mL/min)		
≥80	391/588 (66.5)	130/212 (61.3)
51-79	143/588 (24.3)	58/212 (27.4)
30-49	32/588 (5.4)	18/212 (8.5)
<30	3/588 (0.5)	1/212 (0.5)
Complicating factors		
Males with retention*	33/588 (5.6)	30/212 (14.2)
Indwelling catheter	9/588 (1.5)	7/212 (3.3)
Obstructive uropathy	12/588 (2.0)	6/212 (2.8)
Functional abnormality*	45/588 (7.7)	35/212 (16.5)
Infecting pathogen		
*E. coli**	485/588 (82.5)	144/212 (67.9)
*K. pneumoniae**	32/588 (5.4)	26/212 (12.3)
*P. aeruginosa**	11/588 (1.9)	12/212 (5.7)

* Imbalance between the (non-randomized) groups at the two-sided $\alpha = 0.05$ level.

Table 14: Reviewer's summary of results in the mMITT subset with baseline levofloxacin resistance

Endpoint	Ceftolozane/tazobactam (n = 100)	Levofloxacin (n = 112)	Difference (95% CI)
Composite (TOC)			
Cure	60/100 (60.0)	44/112 (39.3)	20.7 (7.3 to 33.4)
Failure	36/100 (36.0)	64/112 (57.1)	
Indeterminate	4/100 (4.0)	4/112 (3.6)	
Clinical (EOT)			
Cure	94/100 (94.0)	95/112 (84.8)	9.2 (0.9 to 17.8)
Failure	4/100 (4.0)	14/112 (12.5)	
Indeterminate	2/100 (2.0)	3/112 (2.7)	
Clinical (TOC)			
Cure	90/100 (90.0)	86/112 (76.8)	13.2 (3.2 to 23.2)
Failure	8/100 (8.0)	23/112 (20.5)	
Indeterminate	2/100 (2.0)	3/112 (2.7)	
Clinical (LFU)			
Sustained cure	82/100 (82.0)	74/112 (66.1)	15.9 (4.1 to 27.3)
Relapse	7/100 (7.0)	10/112 (8.9)	
Indeterminate	1/100 (1.0)	2/112 (1.8)	
Not applicable	10/100 (10.0)	26/112 (23.2)	
Microbiological (EOT)			
Success	92/100 (92.0)	63/112 (56.2)	35.8 (24.8 to 46.1)
Failure	6/100 (6.0)	36/112 (32.1)	
Non-evaluable	2/100 (2.0)	13/112 (11.6)	
Microbiological (TOC)			
Success	63/100 (63.0)	49/112 (43.8)	19.2 (5.8 to 32.0)
Failure	31/100 (31.0)	56/112 (50.0)	
Non-evaluable	6/100 (6.0)	7/112 (6.2)	
Microbiological (LFU)			
Sustained eradication	12/100 (12.0)	9/112 (8.0)	4.0 (-4.2 to 12.8)
Recurrence	5/100 (5.0)	3/112 (2.7)	
Indeterminate	47/100 (47.0)	41/112 (36.6)	
Not applicable	36/100 (36.0)	59/112 (52.7)	

Table 15: Reviewer's summary of results in the mMITT subset without baseline levofloxacin resistance

Endpoint	Ceftolozane/tazobactam (n = 298)	Levofloxacin (n = 290)	Difference (95% CI)
Composite (TOC)			
Cure	246/298 (82.6)	231/290 (79.7)	2.9 (-3.4 to 9.3)
Failure	30/298 (10.1)	39/290 (13.4)	
Indeterminate	22/298 (7.4)	20/290 (6.9)	
Clinical (EOT)			
Cure	281/298 (94.3)	276/290 (95.2)	-0.9 (-4.7 to 2.9)
Failure	9/298 (3.0)	7/290 (2.4)	
Indeterminate	8/298 (2.7)	7/290 (2.4)	
Clinical (TOC)			
Cure	276/298 (92.6)	270/290 (93.1)	-0.5 (-4.8 to 3.8)
Failure	12/298 (4.0)	12/290 (4.1)	
Indeterminate	10/298 (3.4)	8/290 (2.8)	
Clinical (LFU)			
Sustained cure	266/298 (89.3)	263/290 (90.7)	-1.4 (-6.4 to 3.5)
Relapse	7/298 (2.3)	5/290 (1.7)	
Indeterminate	3/298 (1.0)	2/290 (0.7)	
Not applicable	22/298 (7.4)	20/290 (6.9)	
Microbiological (EOT)			
Success	287/298 (96.3)	277/290 (95.5)	0.8 (-2.6 to 4.3)
Failure	3/298 (1.0)	10/290 (3.4)	
Non-evaluable	8/298 (2.7)	3/290 (1.0)	
Microbiological (TOC)			
Success	257/298 (86.2)	241/290 (83.1)	3.1 (-2.7 to 9.0)
Failure	20/298 (6.7)	29/290 (10.0)	
Non-evaluable	21/298 (7.0)	20/290 (6.9)	
Microbiological (LFU)			
Sustained eradication	41/298 (13.8)	40/290 (13.8)	0.0 (-5.7 to 5.6)
Recurrence	13/298 (4.4)	8/290 (2.8)	
Indeterminate	203/298 (68.1)	195/290 (67.2)	
Not applicable	41/298 (13.8)	47/290 (16.2)	

Among the subset of the mMITT population with levofloxacin resistant baseline pathogens, the study drug was prematurely discontinued for 4/100 (4.0%) subjects in the ceftolozane/tazobactam group and 13/112 (11.6%) subjects in the levofloxacin group. This difference achieved nominal statistical significance (p = 0.04, two-sided).

However, it is notable to this reviewer that the large majority of subjects in the levofloxacin group completed assigned therapy in spite of this resistance, and no subjects

underwent emergency unblinding procedures. Furthermore, only 3/112 (2.7%) of these subjects randomized to levofloxacin were discontinued for the reason listed as "Lack of Efficacy." Therefore, results in this section do not appear to this reviewer to be an artifact of levofloxacin resistance triggering premature discontinuation of study therapy.

The case report forms allowed investigators to classify the reasons for clinical failure as being due to persistence of infection, an adverse event, or other factors. The following table illustrates that persistence of infection was the most common reason for excess failures among levofloxacin treated subjects with levofloxacin resistant pathogens.

Table 16: Reviewer's summary of the reasons for clinical failure at the TOC visit identified by the Applicant (mMITT population)

mMITT subgroup	TOC Clinical Outcome	Ceftolozane/tazobactam (n = 398)	Levofloxacin (n = 402)
Entire mMITT	Failure	20/398 (5.0)	35/402 (8.7)
	Persistence	15/398 (3.8)	29/402 (7.2)
	Adverse event	4/398 (1.0)	4/402 (1.0)
	Other	1/398 (0.3)	2/402 (0.5)
Subset with levofloxacin resistance	Failure	8/100 (8.0)	23/112 (20.5)
	Persistence	6/100 (6.0)	20/112 (17.9)
	Adverse event	1/100 (1.0)	3/112 (2.7)
	Other	1/100 (1.0)	0/112 (0)
Subset without levofloxacin resistance	Failure	12/298 (4.0)	12/290 (4.1)
	Persistence	9/298 (3.0)	9/290 (3.1)
	Adverse event	3/298 (1.0)	1/290 (0.3)
	Other	0/298 (0)	2/290 (0.7)

In summary, this trial enrolled a large proportion of subjects with infecting baseline pathogens resistant to the levofloxacin active control. The overall superiority finding for the primary efficacy analysis appeared to this reviewer to be driven by superior results for ceftolozane/tazobactam on clinical and microbiological outcomes within this subgroup.

3.2.4.4 The impact of indeterminate and missing values

Some subjects in the preceding tables were classified as having indeterminate clinical or microbiological responses, in line with the endpoint categories defined in Section 3.2.1.9 of this review. In the primary analysis, these subjects were considered failures when estimating treatment effects.

To examine the possible impact of incomplete data, this reviewer first considered the most conservative possible sensitivity analysis for assessing treatment effects of ceftolozane/tazobactam: subjects with indeterminate outcomes were considered failures if in the ceftolozane/tazobactam group but were considered successes if they belonged to the levofloxacin group. This form of imputation is conservative because any other method would be more favorable to ceftolozane/tazobactam.

In spite of this conservatism, the table below shows that this reviewer's sensitivity analysis did not change the interpretation of results. No matter how indeterminate data are imputed, ceftolozane/tazobactam will appear superior on clinical and microbiological outcomes at the TOC in the subset with baseline levofloxacin resistance. In the complementary subset of patients without levofloxacin resistance, the lower confidence limit for treatment effects considered below exceeded the original non-inferiority margin of -0.10. Consequently, this reviewer considered the efficacy results to be insensitive to the handling of indeterminate values.

Table 17: Reviewer's sensitivity analysis of indeterminate data (mMITT population)

mMITT subgroup	TOC Outcome	Ceftolozane/ tazobactam	Levofloxacin	Difference (95% CI)
Entire mMITT	Composite cure	306/398 (76.9)	299/402 (74.4)	2.5 (-3.5, 8.5)
	Clinical cure	366/398 (92.0)	367/402 (91.3)	0.7 (-3.2 to 4.6)
	Microbiological success	320/398 (80.4)	317/402 (78.9)	1.5 (-4.1 to 7.1)
Subset with levofloxacin resistance	Composite cure	60/100 (60.0)	48/112 (42.9)	17.1 (3.7 to 30.0)
	Clinical cure	90/100 (90.0)	89/112 (79.5)	10.5 (0.8 to 20.3)
	Microbiological success	63/100 (63.0)	55/112 (49.1)	13.9 (0.5 to 26.8)
Subset without levofloxacin resistance	Composite cure	246/298 (82.6)	251/290 (86.6)	-4.0 (-9.9 to 1.9)
	Clinical cure	276/298 (92.6)	278/290 (95.9)	-3.2 (-7.2 to 0.6)
	Microbiological success	257/298 (86.2)	261/290 (90.0)	-3.8 (-9.1 to 1.5)

3.2.4.5 Subjects without positive baseline cultures

Because a positive microbiological culture at baseline is considered necessary for diagnosing a complicated urinary tract infection, subjects with negative baseline cultures were not necessarily treated with the full study regimens or followed for complete evaluation. Note that microbiological outcomes could not be well-defined for this subgroup. The following table shows that treatment effects on clinical outcomes also could not be assessed within this subset of the randomized patients, due to the amount of incomplete data. Thus, the trial design did not allow for an interpretable assessment of efficacy within this subgroup.

Table 18: Reviewer's analysis of the ITT subgroup not in the mMITT population

Endpoint	Ceftolozane/tazobactam (n = 145)	Levofloxacin (n = 138)	Difference (95% CI)
Clinical (EOT)			
Cure	68/145 (46.9)	77/138 (55.8)	-8.9 (-20.3 to 2.7)
Failure	6/145 (4.1)	10/138 (7.2)	
Indeterminate	59/145 (40.7)	45/138 (32.6)	
Otherwise not available	12/145 (8.3)	6/138 (4.3)	
Clinical (TOC)			
Cure	66/145 (45.5)	67/138 (48.6)	-3.0 (-14.5 to 8.6)
Failure	10/145 (6.9)	17/138 (12.3)	
Indeterminate	57/145 (39.3)	48/138 (34.8)	
Otherwise not available	12/145 (8.3)	6/138 (4.3)	
Clinical (LFU)			
Sustained cure	58/145 (40.0)	59/138 (42.8)	-2.8 (-14.1 to 8.7)
Relapse	2/145 (1.4)	1/138 (0.7)	
Indeterminate	6/145 (4.1)	7/138 (5.1)	
Otherwise not available	79/145 (54.5)	71/138 (51.4)	

3.2.4.6 Pooling of CXA-cUTI-10-04 and CXA-cUTI-10-05

The following table separates results for CXA-cUTI-10-04 and CXA-cUTI-10-05, the two studies that were pooled into the single Phase 3 cUTI trial.

Table 19: Reviewer's comparison of results between the pooled original studies CXA-cUTI-10-04 and CXA-cUTI-10-05

mMITT subgroup	*TOC endpoint*	*Study*	*Ceftolozane/ tazobactam*	*Levofloxacin*	*Difference (95% CI)*
Entire mMITT	Composite cure	10-04	145/198 (73.2)	145/205 (70.7)	2.5 (-6.3 to 11.2)
		10-05	161/200 (80.5)	130/197 (66.0)	14.5 (5.9 to 23.1)
	Clinical cure	10-04	179/198 (90.4)	183/205 (89.3)	1.1 (-4.9 to 7.2)
		10-05	187/200 (93.5)	173/197 (87.8)	5.7 (0.0 to 11.7)
	Microbiological success	10-04	153/198 (77.3)	152/205 (74.1)	3.1 (-5.3 to 11.5)
		10-05	167/200 (83.5)	138/197 (70.1)	13.4 (5.2 to 21.7)

mMITT subgroup	*TOC endpoint*	*Study*	*Ceftolozane/ tazobactam*	*Levofloxacin*	*Difference (95% CI)*
Subset with levofloxacin resistance	Composite cure	10-04	29/54 (53.7)	20/45 (44.4)	9.3 (-10.4 to 28.2)
		10-05	31/46 (67.4)	24/67 (35.8)	31.6 (13.0 to 47.9)
	Clinical cure	10-04	49/54 (90.7)	35/45 (77.8)	13.0 (-1.3 to 28.3)
		10-05	41/46 (89.1)	51/67 (76.1)	13.0 (-1.8, 26.5)
	Microbiological success	10-04	30/54 (55.6)	22/45 (48.9)	6.7 (-12.9 to 25.8)
		10-05	33/46 (71.7)	27/67 (40.3)	31.4 (13.0 to 47.5)
mMITT subgroup	*TOC endpoint*	*Study*	*Ceftolozane/ tazobactam*	*Levofloxacin*	*Difference (95% CI)*
Subset without levofloxacin resistance	Composite cure	10-04	116/144 (80.6)	125/160 (78.1)	2.4 (-6.8 to 11.5)
		10-05	130/154 (84.4)	106/130 (81.5)	2.9 (-5.9 to 11.9)
	Clinical cure	10-04	130/144 (90.3)	148/160 (92.5)	-2.2 (-9.0 to 4.2)
		10-05	146/154 (94.8)	122/130 (93.8)	1.0 (-4.7 to 7.1)
	Microbiological success	10-04	123/144 (85.4)	130/160 (81.2)	4.2 (-4.4 to 12.6)
		10-05	134/154 (87.0)	111/130 (85.4)	1.6 (-6.4 to 10.0)

Within the subgroup without levofloxacin resistant baseline pathogens, results were relatively homogenous between the two studies. There was little noticeable difference between ceftolozane/tazobactam and levofloxacin on clinical or microbiological outcomes in either of CXA-cUTI-10-04 and CXA-cUTI-10-05.

For the subgroup with levofloxacin resistant baseline pathogens, the results were also similar across the two studies in terms of clinical cure results at the TOC visit. In fact, the 13% point estimates for treatment effects were identical between the two studies.

Conversely, within the levofloxacin resistant subgroup there were numerical trends toward heterogeneous outcomes across the studies with respect to microbiological eradication rates. The 31.4% estimated effect between ceftolozane/tazobactam and levofloxacin in CXA-cUTI-10-05 exceeded the 6.7% estimate in CXA-cUTI-10-04. However, in spite of this 31.4%-6.7% = 24.7% difference between estimated treatment effects, this difference between the two estimated effects (i.e., interaction) did not reach the level of statistical significance ($p = 0.07$, two-sided).

The thinking of this reviewer is that the observed heterogeneity between the results in CXA-cUTI-10-04 and CXA-cUTI-10-05 does not necessarily diminish the evidence of efficacy, for several reasons.

First, as previously discussed, from a design perspective the Applicant's pooling of studies was statistically appropriate. The two studies had identical protocols and were conducted in geographically overlapping regions. They were only separated due to the previous FDA recommendation that two trials should be performed for each indication, which was revised such that two trials in related indications (cUTI and cIAI in this application) could provide corroborative evidence. Given that the Applicant was blinded to results at the time of making the decision to pool and finalizing the analysis plan, this reviewer identified no bias or Type I error inflation from the decision to pool.

Second, even if treatment effects differ by study sites, this would not be surprising for a heterogeneous patient population. However, while randomization provides statistical protection against confounding even in the presence of such heterogeneity, this could potentially raise concerns regarding generalizability of results to unstudied US patients.

Third, by chance alone some degree of variation should be expected when examining multiple subgroups. In the subset without levofloxacin resistance, results were consistent between the two studies for both the clinical and microbiological components of the composite endpoint. In the subset with levofloxacin resistance, results were consistent between the two studies for the clinical cure endpoint. The difference in estimated treatment effects on the microbiological endpoint also did not meet the threshold for statistical significance, although sample sizes were small. Overall, this reviewer's view is that there does not appear to be an overwhelming signal for study-level differences.

3.2.4.7 Symptom resolution

This reviewer previously discussed concerns with the Applicant's clinical cure definition and microbiological eradication endpoint in Section 3.2.1.9. Specifically, the components of the Applicant's composite endpoint may not have been sufficiently well-defined and reliable or direct measures of patient benefit. To assess treatment effects on patient feeling and function, this section summarizes effects on urinary symptoms.

Results in this section restrict to the subset of the mMITT population with levofloxacin resistant pathogens at baseline. This review has shown that this subgroup may give the greatest sensitivity for differentiating the treatment arms, and therefore for evaluating whether effects on the Applicant's chosen endpoint translate into improved patient condition. Because the sample size in this subgroup was large enough to allow detection of effects on clinical cure and microbiological endpoints, it should not have impeded detection of treatment effects on symptoms if the effect sizes were of similar magnitude.

Results in the complementary subgroup without levofloxacin resistance are not shown. Unsurprisingly, the subjects in the ceftolozane/tazobactam and levofloxacin groups had similar rates of symptom improvement within this subset.

The symptoms measured in this trial were dysuria, urinary frequency, urinary urgency, flank pain, suprapubic pain, fever with chills or warmth, suprapubic tenderness, costovertebral angle tenderness, and nausea and vomiting. As shown from relevant sections of the Case Report Forms in Figure 3, these symptoms were recorded at baseline as being absent, mild, moderate, or severe. As shown from the Case Report Form in Figure 4, post-baseline assessments involved asking investigators to record whether each symptom was unchanged, worse, or improved relative to the status at the baseline visit.

Table 20 illustrates that symptoms at baseline were relatively well-balanced between the two treatment groups.

Table 22 shows that symptom improvement was relatively similar in the two treatment groups. Despite multiple comparisons considered, the only symptom with significantly greater improvement under ceftolozane/tazobactam was nausea and vomiting.

From Table 22 it is also clear that symptoms generally improved over time from Day 1 through Day 5. However, the rates of improvement were similar in both treatment arms.

These results raise the question of how and why the Applicant's clinical cure endpoint differentiated the two groups in the levofloxacin resistant subset, if they were not greatly differentiated on individual urinary symptoms.

The most disturbing possibility is that the treatment effect on microbiological eradication did not translate to treatment effects on symptomatic patient benefit, but that microbiological results nevertheless influenced the investigators' judgment of resolution.

It is also possible that the symptom measurements were imperfect. Although recorded as absent, mild, moderate, or severe at baseline, the post-baseline measurements of symptoms as improved, unchanged, or worsened may not have been sufficiently granular to detect effects. Further, there may have been recall bias in asking investigators to compare symptoms to the baseline condition. A scale combining symptoms may also have been more sensitive than this reviewer's examination of each symptom in isolation.

It would be speculative to consider whether the results reflect a lack of sensitivity of the symptom measurements or the lack of a large treatment effect on symptomatic improvement. Regardless, this trial does not provide reliable evidence that the effects on the Applicant's chosen endpoint directly translate into symptomatic benefit.

Table 21 displays rates of missing data for the symptom assessments at various times. In this reviewer's analysis, missing values were considered failures. However, there were few subjects in the ceftolozane/tazobactam group with missing symptom measurements. Therefore, even with the most anti-conservative imputation of considering missing values as successful improvement in the ceftolozane/tazobactam group and lack of improvement in the levofloxacin arm, the conclusions would have remained similar.

Figure 3: Baseline symptom assessment

Section 2: Record the current symptom status.	
Dysuria	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐
Frequency	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐
Urgency	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐
Flank Pain	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐
Suprapubic Pain	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐
Fever with complaints of chills, rigors or warmth	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐
Suprapubic tenderness	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐
Costovertebral angle tenderness	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐
Nausea or vomiting	None ☐ Mild ☐ Moderate ☐ Severe ☐ Not Done ☐

Source: Case Report Form.

Figure 4: Post-baseline symptom assesments

Was the symptom assessment performed?	No ☐ Yes ☐
If No, specify reason	_____
Date of Assessment	_____
Prior to Dosing	
Check only one for each of the Symptoms below:	
Assessment of Symptoms (Compare to Baseline)	
Dysuria	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐
Frequency	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐
Urgency	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐
Flank Pain	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐
Suprapubic Pain	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐
Fever with complaints of chills, rigors or warmth	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐
Suprapubic tenderness	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐
Costovertebral angle tenderness	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐
Nausea or Vomiting	Unchanged ☐ Worse ☐ Improved ☐ Not Done ☐

Source: Case Report Form.

Table 20: Reviewer's summary of baseline symptoms in the subset of the mMITT population with a levofloxacin resistant baseline pathogen

Baseline symptom rated as mild, moderate, or severe	Ceftolozane/tazobactam (n = 100)	Levofloxacin (n = 112)
Flank pain	81/100 (81.0)	90/112 (80.4)
Dysuria	76/100 (76.0)	80/112 (71.4)
Urgency	59/100 (59.0)	64/112 (57.1)
Frequency	75/100 (75.0)	77/112 (68.8)
Suprapubic pain	68/100 (68.0)	73/112 (65.2)
Suprapubic tenderness	62/100 (62.0)	64/112 (57.1)
Costovertebral angle tenderness	71/100 (71.0)	74/112 (66.1)
Nausea or vomiting	43/100 (43.0)	45/112 (40.2)
Fever with rigors/chills/warmth	66/100 (66.0)	72/112 (64.3)

Table 21: Reviewer's summary of missing symptom data in the subset of the mMITT population with a levofloxacin resistant baseline pathogen

Ceftolozane/tazobactam (n = 100)							
	Baseline	Day 2	Day 3	Day 4	Day 5	EOT	TOC
Flank pain	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)	2 (2.0)
Dysuria	1 (1.0)	2 (2.0)	3 (3.0)	3 (3.0)	3 (3.0)	2 (2.0)	3 (3.0)
Urgency	1 (1.0)	2 (2.0)	3 (3.0)	3 (3.0)	3 (3.0)	3 (3.0)	4 (4.0)
Frequency	1 (1.0)	2 (2.0)	3 (3.0)	3 (3.0)	3 (3.0)	3 (3.0)	3 (3.0)
Suprapubic pain	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)	2 (2.0)
Suprapubic tenderness	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)	2 (2.0)
Costovertebral angle tenderness	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)	3 (3.0)
Nausea or vomiting	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)	3 (3.0)
Fever with rigors/chills/warmth	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)	2 (2.0)
Levofloxacin (n = 112)							
Flank pain	0 (0.0)	3 (2.7)	5 (4.5)	6 (5.4)	7 (6.2)	2 (1.8)	2 (1.8)
Dysuria	1 (0.9)	4 (3.6)	6 (5.4)	7 (6.2)	7 (6.2)	3 (2.7)	3 (2.7)
Urgency	1 (0.9)	4 (3.6)	6 (5.4)	7 (6.2)	8 (7.1)	3 (2.7)	3 (2.7)
Frequency	1 (1.0)	4 (3.6)	6 (5.4)	7 (6.2)	7 (6.2)	3 (2.7)	4 (4.0)
Suprapubic pain	0 (0.0)	3 (2.7)	5 (4.5)	6 (5.4)	7 (6.2)	2 (1.8)	2 (1.8)
Suprapubic tenderness	0 (0.0)	3 (2.7)	5 (4.5)	6 (5.4)	7 (6.2)	2 (1.8)	2 (1.8)
Costovertebral angle tenderness	0 (0.0)	3 (2.7)	5 (4.5)	6 (5.4)	7 (6.2)	2 (1.8)	2 (1.8)
Nausea or vomiting	0 (0.0)	3 (2.7)	5 (4.5)	6 (5.4)	7 (6.2)	2 (1.8)	2 (1.8)
Fever with rigors/chills/warmth	0 (0.0)	3 (2.7)	5 (4.5)	6 (5.4)	7 (6.2)	2 (1.8)	2 (1.8)

Table 22: Reviewer's summary of improvement from baseline in the subset of the mMITT population with a levofloxacin resistant baseline pathogen. Denominators restrict to subjects with symptoms rated as mild, moderate, or severe at baseline.

Symptom rated as "Improved" from baseline	Ceftolozane/ tazobactam	Levofloxacin	Difference (95% CI)
Flank pain			
Day 2	39/81 (48.1)	43/90 (47.8)	0.4 (-14.5 to 15.2)
Day 3	62/81 (76.5)	70/90 (77.8)	-1.2 (-14.0 to 11.3)
Day 4	70/81 (86.4)	78/90 (86.7)	-0.2 (-11.0 to 10.2)
Day 5	73/81 (90.1)	81/90 (90.0)	0.1 (-9.6 to 9.5)
EOT	78/81 (96.3)	85/90 (94.4)	1.9 (-5.5 to 9.2)
TOC	75/81 (92.6)	85/90 (94.4)	-1.9 (-10.4 to 6.0)
Dysuria			
Day 2	34/76 (44.7)	44/80 (55.0)	-10.3 (-25.4 to 5.4)
Day 3	61/76 (80.3)	64/80 (80.0)	0.3 (-12.5 to 12.9)
Day 4	68/76 (89.5)	73/80 (91.2)	-1.8 (-11.9 to 8.0)
Day 5	72/76 (94.7)	75/80 (93.8)	1.0 (-7.4 to 9.3)
EOT	74/76 (97.4)	74/80 (92.5)	4.9 (-2.5 to 13.2)
TOC	71/76 (93.4)	74/80 (92.5)	0.9 (-8.0 to 9.8)
Urgency			
Day 2	32/59 (54.2)	32/64 (50.0)	4.2 (-13.3 to 21.5)
Day 3	46/59 (78.0)	50/64 (78.1)	-0.2 (-15.1 to 14.5)
Day 4	53/59 (89.8)	55/64 (85.9)	3.9 (-8.3 to 16.0)
Day 5	56/59 (94.9)	56/64 (87.5)	7.4 (-3.1 to 18.5)
EOT	57/59 (96.6)	59/64 (92.2)	4.4 (-4.7 to 14.1)
TOC	55/59 (93.2)	58/64 (90.6)	2.6 (-8.1 to 13.2)
Frequency			
Day 2	36/75 (48.0)	34/77 (44.2)	3.8 (-11.9 to 19.4)
Day 3	58/75 (77.3)	54/77 (70.1)	7.2 (-6.9 to 21.0)
Day 4	68/75 (90.7)	65/77 (84.4)	6.3 (-4.5 to 17.3)
Day 5	72/75 (96.0)	69/77 (89.6)	6.4 (-2.1 to 15.8)
EOT	71/75 (94.7)	68/77 (88.3)	6.4 (-2.8 to 16.2)
TOC	68/75 (90.7)	69/77 (89.6)	1.1 (-9.1 to 11.2)
Suprapubic pain			
Day 2	30/68 (44.1)	31/73 (42.5)	1.7 (-14.5 to 17.8)
Day 3	52/68 (76.5)	51/73 (69.9)	6.6 (-8.1 to 21.0)
Day 4	57/68 (83.8)	58/73 (79.5)	4.4 (-8.7 to 17.3)
Day 5	62/68 (91.2)	62/73 (84.9)	6.2 (-4.9 to 17.5)
EOT	66/68 (97.1)	64/73 (87.7)	9.4 (0.6 to 19.3)
TOC	64/68 (94.1)	66/73 (90.4)	3.7 (-5.9 to 13.5)
Suprapubic tenderness			
Day 2	25/62 (40.3)	26/64 (40.6)	-0.3 (-17.2 to 16.6)
Day 3	46/62 (74.2)	47/64 (73.4)	0.8 (-14.7 to 16.1)
Day 4	49/62 (79.0)	53/64 (82.8)	-3.8 (-17.8 to 10.1)
Day 5	54/62 (87.1)	52/64 (81.2)	5.8 (-7.2 to 19.0)

Symptom rated as "Improved" from baseline	Ceftolozane/ tazobactam	Levofloxacin	Difference (95% CI)
Suprapubic tenderness			
EOT	60/62 (96.8)	56/64 (87.5)	9.3 (-0.2 to 20.0)
TOC	60/62 (96.8)	59/64 (92.2)	4.6 (-4.2 to 14.3)
Costovertebral angle tenderness			
Day 2	35/71 (49.3)	34/74 (45.9)	3.3 (-12.8 to 19.3)
Day 3	58/71 (81.7)	54/74 (73.0)	8.7 (-5.0 to 22.2)
Day 4	65/71 (91.5)	63/74 (85.1)	6.4 (-4.4 to 17.5)
Day 5	66/71 (93.0)	67/74 (90.5)	2.4 (-7.3 to 12.2)
EOT	69/71 (97.2)	69/74 (93.2)	3.9 (-3.8 to 12.4)
TOC	64/71 (90.1)	69/74 (93.2)	-3.1 (-13.2 to 6.4)
Nausea or vomiting			
Day 2	38/43 (88.4)	29/45 (64.4)	23.9 (6.4 to 40.6)
Day 3	39/43 (90.7)	33/45 (73.3)	17.4 (1.3 to 33.3)
Day 4	42/43 (97.7)	38/45 (84.4)	13.2 (1.5 to 26.9)
Day 5	42/43 (97.7)	41/45 (91.1)	6.6 (-4.2 to 18.8)
EOT	43/43 (100)	42/45 (93.3)	6.7 (-1.8 to 17.9)
TOC	42/43 (97.7)	44/45 (97.8)	-0.1 (-10.1 to 9.5)
Fever with rigors, chills, or warmth			
Day 2	42/66 (63.6)	43/72 (59.7)	3.9 (-12.3 to 19.8)
Day 3	54/66 (81.8)	58/72 (80.6)	1.3 (-12.2 to 14.4)
Day 4	61/66 (92.4)	63/72 (87.5)	4.9 (-5.7 to 15.7)
Day 5	63/66 (95.5)	63/72 (87.5)	8.0 (-1.7 to 18.2)
EOT	65/66 (98.5)	68/72 (94.4)	4.0 (-3.1 to 12.1)
TOC	64/66 (97.0)	71/72 (98.6)	-1.6 (-9.2 to 4.8)

3.3 Evaluation of Safety

The primary safety review in this application is deferred to the Medical Officer Maria Allende, M.D.

Only 1 subject died in this Phase 3 trial. This patient was randomized to the ceftolozane/tazobactam group, but the death from a bladder neoplasm on Study Day 4 of treatment was judged by the Applicant and Medical Officer to be unrelated to study drug therapy. There were no deaths in the Applicant's Phase 2 cUTI trial CXA-101-03.

This section presents an additional safety analysis of the subgroup with levofloxacin resistant infections. Specifically, this reviewer assessed whether ceftolozane/tazobactam was associated with a safety advantage relative to levofloxacin in this subgroup, possibly by preventing complications arising from unresolved infections.

Tables 23 and 24 respectively summarize the treatment-emergent serious adverse events (SAEs) and adverse events (AEs) in the subgroup with baseline levofloxacin resistance.

If levofloxacin was indeed ineffective in this group, then its failure to eradicate bacterial pathogens might have translated into higher rates of adverse consequences.

SAEs were rare: it was not possible to statistically differentiate ceftolozane/tazobactam from levofloxacin. Determining the relationship of these events to study drugs would have required a more detailed case analysis beyond the scope of this review.

The overall rates of AEs were similar between ceftolozane/tazobactam and levofloxacin, and likewise there were no statistically meaningful differences seen on rates for specific events or specific organ classes.

Due to the rarity of the adverse events considered and the small sample sizes, these analyses could not exclude the possibility of clinically significant safety differences between the two study drugs. However, these analyses did not demonstrate a safety advantage of ceftolozane/tazobactam relative to levofloxacin for treatment of subjects with levofloxacin resistant infections.

Table 23: Reviewer's summary of treatment emergent serious adverse events for the subset of the mMITT population with a levofloxacin resistant baseline pathogen

SAE event	Ceftolozane/tazobactam (n = 100)	Levofloxacin (n = 112)
Any treatment emergent SAE	5/100 (5.0)	9/112 (8.0)
Immune system disorders	0/100 (0.0)	1/112 (0.9)
Contrast media allergy		
Infections and infestations (total)	3/100 (3.0)	7/112 (6.2)
Pyelonephritis	0/100 (0.0)	3/112 (2.7)
Pyelonephritis acute	0/100 (0.0)	1/112 (0.9)
Sepsis	0/100 (0.0)	1/112 (0.9)
Urinary tract infection	2/100 (2.0)	2/112 (1.8)
Urosepsis	1/100 (1.0)	0/112 (0.0)
Injury, poisoning and procedural complications	0/100 (0.0)	1/112 (0.9)
Pneumothorax traumatic		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2/100 (2.0)	0/112 (0.0)
Bladder cancer		
Renal and urinary disorders (total)	1/100 (1.0)	1/112 (0.9)
Renal colic	1/100 (1.0)	0/112 (0.0)
Renal tubular acidosis	0/100 (0.0)	1/112 (0.9)

Table 24: Reviewer's summary of adverse events for the subset of the mMITT population with a levofloxacin resistant baseline pathogen

AE event	Ceftolozane/tazobactam (n = 100)	Levofloxacin (n = 112)
Any treatment emergent AE	33/100 (33.0)	39/112 (34.8)
Blood and lymphatic system disorders (total)	0/100 (0.0)	3/112 (2.7)
Anaemia	0/100 (0.0)	1/112 (0.9)
Leukocytosis	0/100 (0.0)	2/112 (1.8)
Cardiac disorders	1/100 (1.0)	0/112 (0.0)
Bundle branch block right		
Gastrointestinal disorders (total)	8/100 (8.0)	11/112 (9.8)
Abdominal pain	1/100 (1.0)	0/112 (0.0)
Abdominal pain upper	1/100 (1.0)	2/112 (1.8)
Constipation	4/100 (4.0)	3/112 (2.7))
Diarrhoea	1/100 (1.0)	3/112 (2.7)
Erosive oesophagitis	0/100 (0.0)	1/112 (0.9)
Gastritis	1/100 (1.0)	0/112 (0.0)
Gastritis erosive	0/100 (0.0)	1/112 (0.9)
Hiatus hernia	0/100 (0.0)	1/112 (0.9)
Nausea	1/100 (1.0)	0/112 (0.0)
Pancreatic cyst	1/100 (1.0)	0/112 (0.0)
Salivary hypersecretion	0/100 (0.0)	1/112 (0.9)
Toothache	0/100 (0.0)	1/112 (0.9)
General disorders and administration site conditions (total)	2/100 (2.0)	3/112 (2.7)
Asthenia	0/100 (0.0)	1/112 (0.9)
Chills	0/100 (0.0)	1/112 (0.9)
Infusion site erythema	0/100 (0.0)	1/112 (0.9)
Infusion site oedema	0/100 (0.0)	1/112 (0.9)
Oedema peripheral	1/100 (1.0)	0/112 (0.0)
Suprapubic pain	1/100 (1.0)	0/112 (0.0)
Hepatobiliary disorders (total)	1/100 (1.0)	2/112 (1.8)
Cholecystitis	0/100 (0.0)	2/112 (1.8)
Cholelithiasis	1/100 (1.0)	0/112 (0.0)
Immune system disorders	0/100 (0.0)	1/112 (0.9)
Contrast media allergy		
Infections and infestations (total)	10/100 (10.0)	16/112 (14.3)

Bacteriuria	2/100 (2.0)	3/112 (2.7)
Bronchitis	0/100 (0.0)	1/112 (0.9)
Candidiasis	0/100 (0.0)	1/112 (0.9)
Escherichia urinary tract infection	1/100 (1.0)	1/112 (0.9)
Fungal infection	0/100 (0.0)	1/112 (0.9)
Malaria	1/100 (1.0)	0/112 (0.0)
Nasopharyngitis	1/100 (1.0)	0/112 (0.0)
Pyelonephritis	0/100 (0.0)	3/112 (2.7)
Pyelonephritis acute	0/100 (0.0)	1/112 (0.9)
Sepsis	0/100 (0.0)	1/112 (0.9)
Urinary tract infection	3/100 (3.0)	4/112 (3.6)
Urosepsis	1/100 (1.0)	0/112 (0.0)
Vulvovaginal candidiasis	1/100 (1.0)	0/112 (0.0)
Injury, poisoning and procedural complications (total)	1/100 (1.0)	1/112 (0.9)
Excoriation	1/100 (1.0)	0/112 (0.0)
Pneumothorax traumatic	0/100 (0.0)	1/112 (0.9)
Investigations (total)	0/100 (0.0)	1/112 (0.9)
Alanine aminotransferase increased	0/100 (0.0)	1/112 (0.9)
Blood alkaline phosphatase increased	0/100 (0.0)	1/112 (0.9)
Metabolism and nutrition disorders (total)	3/100 (3.0)	3/112 (2.7)
Decreased appetite	1/100 (1.0)	0/112 (0.0)
Diabetes mellitus	0/100 (0.0)	1/112 (0.9)
Hyperglycaemia	1/100 (1.0)	0/112 (0.0)
Hypoalbuminaemia	0/100 (0.0)	1/112 (0.9)
Hypoglycaemia	1/100 (1.0)	0/112 (0.0)
Hypokalaemia	0/100 (0.0)	1/112 (0.9)
Musculoskeletal and connective tissue disorders (total)	2/100 (2.0)	3/112 (2.7)
Arthralgia	0/100 (0.0)	1/112 (0.9)
Back pain	1/100 (1.0)	0/112 (0.0)
Haemarthrosis	0/100 (0.0)	1/112 (0.9)
Musculoskeletal pain	0/100 (0.0)	1/112 (0.9)
Myalgia	1/100 (1.0)	1/112 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2/100 (2.0)	0/112 (0.0)
Bladder cancer		
Nervous system disorders (total)	3/100 (3.0)	6/112 (5.4)
Epilepsy	0/100 (0.0)	1/112 (0.9)
Headache	2/100 (2.0)	5/112 (4.5)

Migraine	1/100 (1.0)	0/112 (0.0)
Psychiatric disorders (total)	2/100 (2.0)	6/112 (5.4)
Insomnia	2/100 (2.0)	6/112 (5.4)
Nightmare	0/100 (0.0)	1/112 (0.9)
Renal and urinary disorders (total)	8/100 (8.0)	7/112 (6.2)
Haematuria	1/100 (1.0)	1/112 (0.9)
Leukocyturia	1/100 (1.0)	2/112 (1.8)
Nephropathy	0/100 (0.0)	1/112 (0.9)
Pollakiuria	0/100 (0.0)	1/112 (0.9)
Pyelocaliectasis	1/100 (1.0)	0/112 (0.0)
Pyuria	1/100 (1.0)	0/112 (0.0)
Renal colic	1/100 (1.0)	0/112 (0.0)
Renal cyst	1/100 (1.0)	0/112 (0.0)
Renal impairment	1/100 (1.0)	1/112 (0.9)
Renal tubular acidosis	0/100 (0.0)	1/112 (0.9)
Urinary retention	1/100 (1.0)	0/112 (0.0)
Reproductive system and breast disorders	1/100 (1.0)	0/112 (0.0)
Prostatomegaly		
Respiratory, thoracic, and mediastinal disorders	1/100 (1.0)	1/112 (0.9)
Cough		
Skin and subcutaneous tissue disorders	3/100 (3.0)	1/112 (0.9)
Erythema	0/100 (0.0)	1/112 (0.9)
Pruritus	1/100 (1.0)	0/112 (0.0)
Rash	2/100 (2.0)	0/112 (0.0)
Vascular disorders	7/100 (7.0)	3/112 (2.7)
Blood pressure inadequately controlled	0/100 (0.0)	1/112 (0.9)
Hypertension	5/100 (5.0)	0/112 (0.0)
Hypotension	1/100 (1.0)	0/112 (0.0)
Phlebitis	1/100 (1.0)	1/112 (0.9)
Thrombophlebitis	0/100 (0.0)	1/112 (0.9)

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 25 presents results for demographic subgroups of the primary mMITT analysis population. The table separates subjects with and without baseline levofloxacin resistance, and reports results for the composite clinical and microbiological outcome at the TOC visit that was used as the Applicant's primary efficacy endpoint.

When infecting baseline pathogens were levofloxacin resistant, ceftolozane/tazobactam consistently led to higher response rates than the levofloxacin control across demographic subgroups.

Conversely, when infecting pathogens were not resistant to levofloxacin, the two groups generally appeared to give similar results across these subgroups.

4.2 Other Special/Subgroup Populations

Table 26 displays results for baseline subgroups of the mMITT population defined by disease type (pyelonephritis or cLUTI), creatinine clearance, and bacteremia.

Because there were few subjects with bacteremia or impaired renal function, efficacy in these important patient subsets could not be precisely characterized in this trial.

The most notable finding from the table concerned differences between subjects with pyelonephritis and cLUTI. There was near uniform failure of the levofloxacin group among subjects with cLUTI and levofloxacin resistant pathogens. While it is possible that an overwhelming effect size in this group may have driven the overall superiority finding, this hypothesis should be considered exploratory due to the small sample sizes involved and the conduct of multiple post-hoc comparisons.

Finally, Table 27 shows results for subgroups defined by different infecting baseline pathogens. The four pathogens displayed are *E. coli, K. pneumoniae, P. aeruginosa,* and *P. mirabilis*. Together, the subjects infected with these pathogens accounted for 727/800 (90.9%) of the mMITT primary analysis population.

Results for the *E. coli* subgroup mirrored the overall results, with trends toward superior results for ceftolozane/tazobactam in the levofloxacin resistant subset, with similarity between the two treatment groups in the subset without levofloxacin resistance.

For the other pathogens considered in the table, results were limited by small sample sizes but trends were generally supportive of overall efficacy.

Although the Applicant has noted that ceftolozane/tazobactam was developed in large part as therapy for *P. aeruginosa* infections, only 8 mMITT subjects were treated with the drug, and 6/8 achieved both clinical and microbiological response at the TOC visit.

There are some additional pseudomonal data from the Phase 2 trial previously discussed in Section 2.1.3 of this review, CXA-101-03. At baseline, 5 subjects had *P. aeruginosa* infections, all 5 were randomized to the ceftolozane/tazobactam group, all 5 met this trial's clinical cure criteria, and 3/5 achieved microbiological eradication criteria.

Table 25: Reviewer's summary of subgroup results for demographic factors on the composite clinical and microbiological response at TOC (mMITT population)

mMITT subgroup (Levofloxacin resistant)	*Ceftolozane/ tazobactam*	*Levofloxacin*	*Difference (95% CI)*
Sex			
Male	29/50 (58.0)	13/40 (32.5)	25.5 (4.8 to 44.0)
Female	31/50 (62.0)	31.72 (43.1)	18.9 (0.9 to 35.7)
Race			
White	44/78 (56.4)	37/95 (38.9)	17.5 (2.5 to 31.7)
Other	16/22 (72.7)	7/17 (41.2)	31.6 (0.4 to 57.5)
Age			
18-44	13/24 (54.2)	21/38 (55.3)	-1.1 (-25.8 to 23.3)
45-64	28/46 (60.9)	12/33 (36.4)	24.5 (2.2 to 44.4)
≥65	19/30 (63.3)	11/41 (26.8)	36.5 (13.3 to 56.1)
Region			
Eastern Europe	39/69 (56.5)	30/83 (36.1)	20.4 (4.5 to 35.3)
United States	2/2 (100)	1/1 (100)	0 (-65.8 to 79.3)
Other	19/29 (65.5)	13/28 (46.4)	19.1 (-6.6 to 42.5)
mMITT subgroup (Not levofloxacin resistant)	*Ceftolozane/ tazobactam*	*Levofloxacin*	*Difference (95% CI)*
Sex			
Male	40/55 (72.7)	46/63 (73.0)	-0.3 (-16.5 to 15.6)
Female	206/243 (84.8)	185/227 (81.5)	3.3 (-3.5 to 10.2)
Race			
White	217/262 (82.8)	202/251 (80.5)	2.3 (-4.4 to 9.1)
Other	29/36 (80.6)	29/39 (74.4)	6.2 (-13.2 to 25.0)
Age			
18-44	129/141 (91.5)	120/144 (83.3)	8.2 (0.5 to 16.1)
45-64	66/87 (75.9)	69/88 (78.4)	-2.5 (-15.1 to 10.0)
≥65	51/70 (72.9)	42/58 (72.4)	0.4 (-14.8 to 16.2)
Region			
Eastern Europe	196/235 (83.4)	183/221 (82.8)	0.6 (-6.3 to 7.6)
United States	3/7 (42.9)	3/4 (75.0)	-32.1 (-71.9 to 27.0)
Other	47/56 (83.9)	45/65 (69.2)	14.7 (-0.6 to 29.2)

Table 26: Reviewer's additional subgroup summary on the composite clinical and microbiological outcome at TOC (mMITT population)

mMITT subgroup (Levofloxacin resistant)	*Ceftolozane/ tazobactam*	*Levofloxacin*	*Difference (95% CI)*
Baseline diagnosis			
Pyelonephritis	43/71 (60.6)	39/77 (50.6)	9.9 (-6.1 to 25.4)
cLUTI	17/29 (58.6)	5/35 (14.3)	44.3 (21.5 to 63.2)
Creatinine clearance			
≤50 mL/min	6/12 (50.0)	1/10 (10.0)	40.0 (1.0 to 68.2)
>50 mL/min	54/88 (61.4)	43/102 (42.2)	19.2 (5.0 to 32.7)
Bactermic status			
Bacteremic	1/2 (50.0)	2/5 (40.0)	10.0 (-53.1 to 67.9)
Non-bacteremic	59/98 (60.2)	42/107 (39.3)	21.0 (7.3 to 33.8)
mMITT subgroup (Not levofloxacin resistant)	*Ceftolozane/ tazobactam*	*Levofloxacin*	*Difference (95% CI)*
Baseline diagnosis			
Pyelonephritis	216/257 (84.0)	201/251 (80.1)	4.0 (-2.7 to 10.7)
cLUTI	30/41 (73.2)	30/39 (76.9)	-3.8 (-22.6 to 15.5)
Creatinine clearance			
≤50 mL/min	15/22 (68.2)	16/18 (88.9)	-20.7 (-44.3 to 5.9)
>50 mL/min	231/275 (84.0)	215/272 (79.0)	5.0 (-1.6 to 11.5)
Bactermic status			
Bacteremic	22/27 (81.5)	17/28 (60.7)	20.8 (-3.3 to 42.9)
Non-bacteremic	224/271 (82.7)	214/262 (81.7)	1.0 (-5.5 to 7.5)

Table 27: Reviewer's summary of subgroup results by baseline pathogens on the composite clinical and microbiological outcome at TOC (mMITT population)

Pathogen subgroup	Ceftolozane/tazobactam	Levofloxacin
Escherichia coli		
Entire mMITT subgroup	247/305 (81.0)	228/324 (70.4)
Levofloxacin resistance	43/66 (65.2)	29/78 (37.2)
No levofloxacin resistance	204/239 (85.4)	199/246 (80.9)
Klebsiella pneumoniae		
Entire mMITT subgroup	22/33 (66.7)	12/25 (48.0)
Levofloxacin resistance	9/13 (69.2)	3/11 (27.3)
No levofloxacin resistance	13/20 (65.0)	9/14 (64.3)
Pseudomonas aeruginosa		
Entire mMITT subgroup	6/8 (75.0)	7/15 (46.7)
Levofloxacin resistance	3/4 (75.0)	2/8 (25.0)
No levofloxacin resistance	3/4 (75.0)	5/7 (71.4)
Proteus mirabilis		
Entire mMITT subgroup	11/12 (91.7)	6/12 (50.0)
Levofloxacin resistance	0/0	2/2 (100)
No levofloxacin resistance	11/12 (91.7)	4/10 (40.0)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This reviewer analyzed the single Phase 3 trial conducted by the Applicant in subjects with complicated urinary tract infections. Supportive evidence of safety and efficacy was to be generated through a separate Phase 3 trial in another indication, evaluating ceftolozane/tazobactam for the treatment of complicated intra-abdominal infections.

The cUTI trial design elements and statistical analysis plan were generally consistent with recommendations in the 2012 FDA guidance document. The trial enrolled subjects with either pyelonephritis or cLUTI who had signs and symptoms of infection, and was predominately conducted in the Eastern European region. This randomized study compared 7-day intravenous ceftolozane/tazobactam to 7-day intravenous levofloxacin, was double-blinded, and did not allow prior antibacterial therapy except in limited circumstances. The primary efficacy analysis population required microbiologically confirmed infection from a baseline specimen, and the primary efficacy endpoint was a composite requiring both investigator assessment of clinical resolution and microbiological eradication at the TOC visit 7 ± 2 days following the end of therapy.

Although designed as a non-inferiority trial, ceftolozane/tazobactam met statistical criteria for superiority relative to levofloxacin with respect to the primary efficacy endpoint. This provided relatively strong evidence for a treatment effect on this endpoint. This reviewer considers superiority findings to be inherently more interpretable than non-inferiority findings, which are limited by untestable assumptions.

Post-hoc exploration of results revealed the likely reason why the superiority demonstration was possible: many subjects were infected by baseline pathogens resistant to the levofloxacin comparator. In subjects with levofloxacin resistance there was a large treatment effect favoring ceftolozane/tazobactam on both the clinical and microbiological components of the composite primary endpoint, while the two study drugs yielded similar results in the subgroup without baseline levofloxacin resistance.

One issue considered in this review concerned the fact that the Phase 3 trial was originally designed as two separate cUTI studies, which were then pooled. Because the studies were pooled while the sponsor was blinded to results and the studies had identical protocols, this reviewer did not identify possible biases from this decision. Results across the two studies were similar in the subgroup without baseline levofloxacin resistance, and were also similar for the Applicant's clinical cure endpoint in the subgroup with baseline levofloxacin resistance. Although there was some degree of observed treatment effect heterogeneity across the two studies with respect to the Applicant's microbiological eradication endpoint, this heterogeneity did not reach the level of statistical significance. This reviewer did not consider the pooling to have compromised the efficacy conclusions.

Some subjects in this trial were classified by the Applicant as having indeterminate clinical or microbiological outcomes. This reviewer found the efficacy results to be robust to the handling of indeterminate data. Even with the imputation method least favorable to ceftolozane/tazobactam the results would have yielded the same interpretation, with statistically superior results for ceftolozane/tazobactam on clinical and microbiological endpoints in the subgroup with baseline levofloxacin resistance, but no trends toward superiority in the subgroup without levofloxacin resistance.

There were several limitations of this trial. There was minimal enrollment of subjects from the United States, and therefore generalizability to the US patient population would require extrapolation.

Another review issue was the Applicant's choice of primary efficacy endpoint, because the clinical and microbiological components of the composite may have been either poorly defined or indirect measures of patient benefit. Consequently, this reviewer assessed whether there was a treatment effect for ceftolozane/tazobactam on the major symptoms of cUTI. Even in the subgroup with baseline levofloxacin resistance, this trial did not provide evidence that ceftolozane/tazobactam led to improved symptom resolution compared to levofloxacin. However, it was unclear whether this reflected a genuine lack of treatment benefit or insensitivity of the symptom measurements and methods of analysis. In addition, this trial did not provide statistical evidence of a safety advantage for ceftolozane/tazobactam in the subgroup with levofloxacin resistance, even though complications might have been expected from unresolved infections. Therefore, it remained unclear whether ceftolozane/tazobactam led to better results than levofloxacin on clinically meaningful outcomes, or whether the Applicant's superiority finding was driven by effects on measures that were of limited consequence to patients.

5.2 Conclusions and Recommendations

This reviewer's overall conclusions and recommendations are as follows:

- The reviewed Phase 3 trial provided evidence for a treatment effect of ceftolozane/tazobactam on the Applicant's composite primary efficacy endpoint, requiring investigator judgment of resolution and microbiological eradication of the infecting pathogen at the TOC visit 7 ± 2 days following the end of therapy.
- There was evidence of effect modification. Ceftolozane/tazobactam appeared to give higher success rates than levofloxacin on the clinical and microbiological components of the Applicant's endpoint in the subgroup with baseline pathogens that were resistant to levofloxacin. Conversely, the two study drugs appeared to perform similarly in the subgroup without levofloxacin resistance.
- The interpretation of results was robust to handling of indeterminate values for the Applicant's clinical and microbiological endpoints.
- The reviewed Phase 3 trial was originally designed as two separate studies, which were then pooled, but the pooling and resulting level of heterogeneity did not appear to compromise or limit interpretation of the efficacy results.

- For this trial conducted predominately in Eastern Europe, generalizability to patients in the United States was limited by the enrollment of only 14 US subjects in the Applicant's primary efficacy analysis population.
- Even in the subgroup with levofloxacin resistant baseline pathogens, the trial did not provide statistical evidence that ceftolozane/tazobactam led to improved rates of symptom resolution compared to levofloxacin, nor to an improved safety profile. Thus, despite the superiority findings on the primary endpoint, the patient benefit from ceftolozane/tazobactam in this subgroup remains unclear.

5.3 Labeling Recommendations

The italicized text below copies the Applicant's originally proposed text for the CLINICAL STUDIES section of the label. This section will govern how results of the cUTI trial can be marketed by the Applicant, and according to FDA guidance[6] should "include information from the adequate and well-controlled studies that demonstrate the effectiveness of the drug for its approved indication." Note that ZERBAXA is the Applicant's proposed trade name for ceftolozane/tazobactam.

(b) (4)

[6] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127534.pdf. Accessed August 15, 2014.

(b) (4)

One concern with the Applicant's proposal relates to the 2006 FDA guidance on the

(b) (4)

(b) (4)

(b) (4)

Therefore, this reviewer recommends replacing the Applicant's phrase (b) (4) by "ZERBAXA demonstrated efficacy with regard to the composite…"

Because the aforementioned guidance also calls for the CLINICAL STUDIES section of the label to summarize "the important limitations of the available evidence," this reviewer recommends that the trial description summarize the majority enrollment from the Eastern European region and the limited enrollment from the United States.

As (b) (4) the label is meant to include results supported by substantial evidence, this reviewer further recommends that the label remove the (b) (4)

This reviewer also has several recommendations to improve the display of results in subgroups defined by baseline pathogen in the Applicant's proposed (b) (4) As discussed in Section 3.2.1.8 of this review, the mMITT population used for the primary efficacy analysis was comprised of randomized subjects who received at least one dose of study drug and had microbiologically confirmed infection from a baseline specimen. The mMITT population was considered by this reviewer to be protected from confounding by randomization, (b) (4) Hence, this reviewer recommends that any display of results for subgroups defined by baseline pathogens use subgroups of the mMITT analysis population. Further, the Applicant's proposed (b) (4) consists of (b) (4) Thus, this reviewer recommends that any display of results for subgroups defined by baseline pathogens instead present "per patient" analyses. The Applicant's proposed (b) (4) states that the CLINICAL STUDIES "section must not suggest or imply indications, uses or dosing regimens not stated in the INDICATIONS AND USAGE" section of the label, which governs the overall claim of safety and efficacy supported by application. This reviewer defers to the Medical Officer and to the clinical microbiologically reviewer regarding whether ceftolozane/tazobactam should be indicated for treatment of cUTI due to (b) (4)

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/s/

DANIEL B RUBIN
09/23/2014

THAMBAN I VALAPPIL
09/24/2014

DIONNE L PRICE
10/04/2014
Concur with overall conclusion. Please see tertiary memo/review for an additional comment.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206829 **Applicant: Cubist Pharmaceuticals** **Stamp Date: 4/21/14**

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

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			ISE is not applicable
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	**Yes**	**No**	**NA**	**Comment**
Designs utilized are appropriate for the indications requested.	**X**			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**X**			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			**X**	**Interim analyses are not present**
Appropriate references for novel statistical methodology (if present) **X** are included.	**X**			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Safety data organized to permit analyses across clinical trials in the NDA/BLA.			**X**	**My review will not perform pooled safety analyses**
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	**X**			**Various approaches are defined for imputing missing data.**

Brief summary of controlled clinical trials
The following table contains information on the relevant trials contained in the submission.

Study Number	Design	Planned Sample Size	Primary endpoint	Sponsor's findings
CXA-cIAI-10-08&09	Phase 3, randomized, double-blind, multicenter, non-inferiority trial comparing ceftolozane/tazobactam plus metronidazole to meropenem for the treatment of subjects with cIAI.	988 patients randomized 1:1 (494 per arm), 790 micro-ITT (MITT) patients (395 per arm)	Clinical cure rate at the TOC visit (24-32 days after initiation of study drug) in the primary MITT population . The MITT included all randomized subjects who had IAI as evidenced by identification of at least 1 baseline intra-abdominal pathogen, regardless to susceptibility to study drug.	According to the Sponsor, this study met its pre-defined primary endpoint based on a 10% NI margin. The weighted difference in clinical cure rates ([ceftolozane/tazobactam plus metronidazole] minus meropenem) was -4.2% with a 2-sided 95% CI of (-8.9%, 0.5%).

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/s/

CHRISTOPHER E KADOORIE
06/16/2014

THAMBAN I VALAPPIL
06/16/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206829 **Applicant: Cubist Pharmaceuticals** **Stamp Date: 04/21/2014**

Drug: Ceftolozane/tazobactam **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Acceptable on initial review
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			Acceptable on initial review
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No data monitoring committee was convened and no interim analyses were performed
Appropriate references for novel statistical methodology (if present) are included.			X	The statistical methodology was relatively straightforward

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	My review will not pool results across trials conducted in different indications
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			Acceptable on initial review

Brief summary of controlled clinical trials
The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
10-04-10-05.	This was a Phase 3, randomized, double-blind, multicenter, non-inferiority trial that compared ceftolozane/tazobactam to levofloxacin for the treatment of subjects with complicated urinary tract infections, including pyelonephritis.	This trial used 1:1 randomization of 1083 total subjects to either intravenous ceftolozane/tazobactam or to intravenous levofloxacin.	The primary efficacy endpoint was a composite requiring microbiological eradication of the uropathogen and investigator assessed clinical cure at the test of cure visit, approximately 7 days after the end of therapy. The primary analysis population was comprised of all randomized subjects who received any amount of study drug and who had a baseline uropathogen.	Even though this was designed as a non-inferiority trial, the primary analysis showed a statistically significant difference in favor of ceftolozane/tazobactam with respect to the primary efficacy endpoint. The sponsor concluded that ceftolozane/tazobactam compared favorably to levofloxacin for this indication.

Daniel Rubin **06/05/2014**
Reviewing Statistician Date

Dionne Price **06/05/2014**
Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

DANIEL B RUBIN
06/10/2014

DIONNE L PRICE
06/11/2014
Signing on behalf of the team leader who is on leave.