Official Protocol Title:	A Phase 3, Multicenter, Double-blind, Randomized, Active-controlled Clinical Study to Evaluate the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) plus Metronidazole Versus Meropenem in Chinese Participants with Complicated Intraabdominal Infection
NCT number:	NCT03830333
Document Date:	24-JUL-2020

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Phase 3, Multicenter, Double-blind, Randomized, Active-controlled Clinical Study to Evaluate the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) plus Metronidazole Versus Meropenem in Chinese Participants with Complicated Intra-abdominal Infection

Protocol Number: 015-02

Compound Number: MK-7625A

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

Approval Date: 24 July 2020

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
7625A-015-02	24-JUL-2020	Amendment 02
7625A-015-01	17-JAN-2020	Amendment 01
7625A-015-00	11-SEP-2018	Original Protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

Update the allowed contraceptive methods according to the TransCelerate Common Protocol Template guidelines for contraception and pregnancy testing based upon Clinical Trial Facilitation Group (CTFG) recommendations.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria 10.5.2 Contraception Requirements	To update the contraceptive requirements with updated template wording in the inclusion criteria and the allowed contraceptive methods to highly effective methods in Appendix 5.	For alignment with recent revisions to the TransCelerate Common Protocol Template guidelines for contraception and pregnancy testing based upon CTFG recommendations.
1.3 Schedule of Activities Urine for Urinalysis	Added footnote “d” to “Urine for Urinalysis” at Screening.	Urinalysis performed prior to signing the informed consent may be used if collected during the routine care of the patient, as long as they were conducted within 24 hours prior to randomization.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Multicenter, Double-blind, Randomized, Active-controlled Clinical Study to Evaluate the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) plus Metronidazole Versus Meropenem in Chinese Participants with Complicated Intra-abdominal Infection

Short Title: MK-7625A plus Metronidazole vs. Meropenem for China Participants with cIAI

Acronym: 7625A CN Phase3

Hypotheses, Objectives, and Endpoints:

The following objectives and endpoints will be evaluated in adult participants diagnosed with complicated intra-abdominal infection (cIAI).

Objectives	Endpoints
Primary	
• **Objectives:** To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to clinical response at the test of cure (TOC) visit for participants diagnosed with cIAI in the clinically evaluable (CE) population. **Hypothesis:** Ceftolozane/tazobactam plus metronizazole is non-inferior to meropenem in participants with cIAI, as measured by the clinical response rate at TOC visit in the CE population.	• Clinical response: A favorable clinical response is clinical cure (see Section 8.2.1).
Secondary	

• Objective: To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to clinical response for participants diagnosed with cIAI.
  • Clinical response at the TOC visit in the intent-to-treat (ITT) population
  • Clinical response at the end of therapy (EOT) visit in the ITT and CE population
	• Clinical response

Objectives	Endpoints

• Objective: To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to microbiological response for participants diagnosed with cIAI
  • Per-subject microbiological response at the TOC visit in the expanded microbiologically evaluable (EME) population
  • Per-pathogen microbiological response at the TOC visit in the EME population
	• Per-subject microbiological response: For a favorable overall microbiological response (i.e., eradication or presumed eradication), each baseline pathogen for the participant must have a favorable microbiological outcome (see Section 8.2.2).
	• Per-pathogen microbiological response: A favorable microbiological responses include “eradication” or “presumed eradication” (see Section 8.2.2).

• Objective: To evaluate the safety and tolerability of ceftolozane/tazobactam plus metronizazole in participants diagnosed with cIAI.	• Adverse events (AEs) • Study treatment discountinuation due to AE
Exploratory	

• Objective: To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to clinical response for participants diagnosed with cIAI.
  • Clinical response at TOC visit in the microbiological intent-to-treat (MITT) population and microbiologically evaluable (ME) population
  • Clinical response at EOT visit in the MITT population
	• Clinical response

Objectives	Endpoints

• Objective: To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to microbiological response for participants diagnosed with cIAI.
  • Per-subject microbiological response at the TOC visit in the ME and MITT population
  • Per-subject microbiological response at the EOT visit in the ME, EME and MITT population
  • Per-pathogen microbiological response at the TOC visit in the ME and MITT population
  • Per-pathogen microbiological response at the EOT visit in the ME, EME and MITT population
	• Per-subject microbiological response
	• Per-pathogen microbiological response

TOC = test of cure; EOT = end of therapy; CE = clinically evaluable; ITT = intent-to-treat; MITT = microbiological intent-to-treat; ME= microbiologically evaluable; EME = expanded ME

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Complicated Intra-abdominal Infections
Population	Adult patients with cIAI
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control plus placebo
Study Blinding	Double-blind
Masking	Participant; Investigator; Outcomes Assessor; Data Analyst
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 20 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 268 participants will be randomized to obtain 200 evaluable participants as described in Section 9.9.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
1	ceftolozane/ tazobactam	1500 mg (ceftolozane 1000 mg /tazobactam 500 mg) 750 mg† (ceftolozane 500 mg /tazobactam 250 mg)	q8h	IV infusion	60 min intravenous infusion/4-14 days	Study drug
	Metronidazole	500 mg	q8h	IV infusion	60 min intravenous infusion/4-14 days	Concomitant drug
2	Meropenem	1000 mg	q8h OR q12h†	IV infusion	60 min intravenous infusion/4-14 days	Comparator
	Saline	NA	q8h	IV infusion	60 min intravenous infusion/4-14 days	Placebo

Abbreviations: q8h=every 8 hours; IV=intravenous; NA=not applicable; q12h=every 12 hours.
†For participants with CrCL :30 to ≤ 50 mL/min.
In order to maintain double dummy of the study, the placebo (saline) need to be administered in the participant with CrCL 30 to ≤50 mL/min in both arms.

Total Number	Two groups
Duration of Participation	Each participant will participate in the study for approximately 31 days at maximum from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of maximal 24 hours, each participant will receive ceftolozane/tazobactam plus metronidazole, or meropenem plus placebo for 4-14 days. An End-of Treatment (EOT) visit will be performed within 24 hours after the last dose of study drug, a Test-of-Cure (TOC) will be performed at 26 to 30 days after the first dose of study drug. All adverse events (AEs) and serious adverse events (SAEs) will be reported by the investigator through the TOC evaluation.

Study Governance Committees:

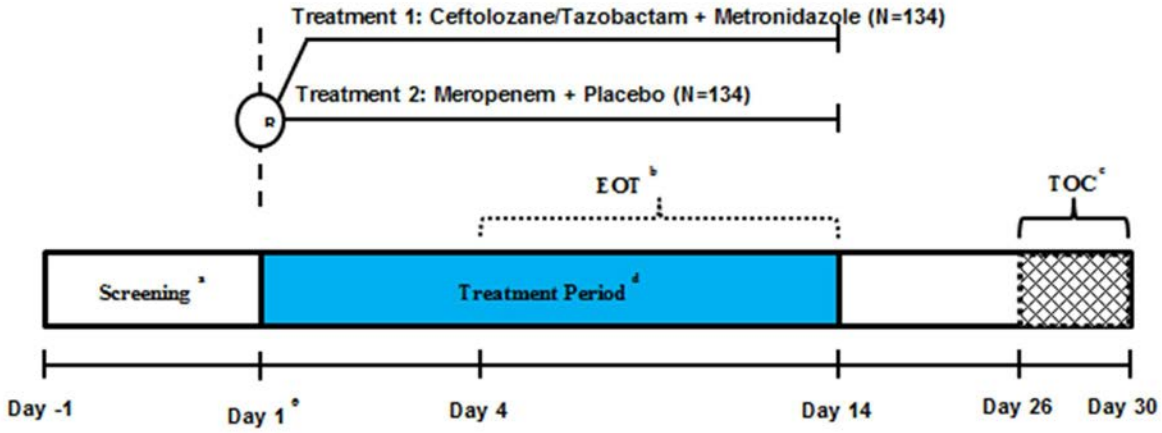
Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.



Randomization will be stratified by anatomic site of infection (bowel [small or large] vs. other site of cIAI).
EOT = end of therapy, TOC = test of cure
[a] The screening visit must occur ≤ 24 hours prior to randomization.
[b] The EOT visit must occur ≤ 24 hours after the last dose of IV study therapy.
[c] The TOC visit is the Day 28 after first dose of study drug administration (Day 26 to Day 30 is allowed for time window).
[d] Total duration of study drug treatment will be 4 to 14 days.
[e] There is no day 0 in this study.

Figure 1 Study Design

1.3 Schedule of Activities (SoA)

Study Period	**Screening**	**Intervention**					**Post-treatment**	**Notes**
Visit Number/Title	1 Screening	2 Randomization	**3**	**4**	**5**	6 (EOT)	7 (TOC)	Visit 1 and Visit 2 can be done on the same day. If treatment ends before Day 14, then will go to the Visit 6 directly for EOT visit.
Scheduled Hour and Day:	≤ 24 hours prior to randomization	Day 1	Day 2	Day 3	Day 4-13	Day 14 /EOT/Early Discontinuation visit	Day 28	
Scheduling Window:		-	-	-	-	+24 hrs	±2 days	
Administrative Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Participant Identification Card	X							
Medical History	X							
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	
Intervention Allocation or Randomization		X						
Ceftolozane/tazobactam + metronidazole OR meropenem + placebo Administration/Dispensing		Daily administered IV						IV study medication cannot be changed to oral antibiotics.
Efficacy Procedures								
Clinical Response Assessment (Assessment of clinical outcome)						X	X	

Study Period	**Screening**	**Intervention**					**Post-treatment**	**Notes**
Visit Number/Title	1 Screening	2 Randomization	**3**	**4**	**5**	6 (EOT)	7 (TOC)	Visit 1 and Visit 2 can be done on the same day. If treatment ends before Day 14, then will go to the Visit 6 directly for EOT visit.
Scheduled Hour and Day:	≤ 24 hours prior to randomization	Day 1	Day 2	Day 3	Day 4-13	Day 14 /EOT/Early Discontinuation visit	Day 28	
Scheduling Window:		-	-	-	-	+24 hrs	±2 days	
Clinical and Safety Procedures/Assessments								
Full physical examination	X					X[a]		
Directed Physical Examination		Daily at the discretion of the investigator					X	
Skin test	X							If required by local clinical regulations, skin test will be conducted during screening if no prior history of allergic reaction to beta-lactam antibacterial.
Vital Signs (pulse rate, blood pressure, temperature, respiratory rate)	X[d]	Daily during IV study therapy				X	X	
Height and Weight	X[d]							
Surgical Wound Examination	X	Daily during IV study therapy				X	X	The surgical wound examination will be performed and findings are recorded only for participants who have a surgical wound.
APACHE II Score	X[d]							
Abdominal symptoms and signs	X[d]	Daily during IV study therapy				X	X	

Study Period	**Screening**	**Intervention**					**Post-treatment**	**Notes**
Visit Number/Title	1 Screening	2 Randomization	**3**	**4**	**5**	6 (EOT)	7 (TOC)	Visit 1 and Visit 2 can be done on the same day. If treatment ends before Day 14, then will go to the Visit 6 directly for EOT visit.
Scheduled Hour and Day:	≤ 24 hours prior to randomization	Day 1	Day 2	Day 3	Day 4-13	Day 14 /EOT/Early Discontinuation visit	Day 28	
Scheduling Window:		-	-	-	-	+24 hrs	±2 days	
Radiographic examination (Ultrasound, X-ray or CT etc.)	X[a, d]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	
Diagnosis of target disease and site of infection	X							
Record blood or blood product transfusions	X	X	X	X	X	X	X	
Record summary of operative procedures and operative notes	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	
AE/SAE review	X	Daily during IV study therapy				X	X	AEs/SAEs and other reportable safety events must be reported by the investigator from the time of informed consent through TOC visit.
Laboratory Procedures/Assessments								
Serum Pregnancy Test (Woman of Childbearing Potential [WOCBP] only)	X						X	Prior documentation of a negative serum β-HCG within 48 hours of enrollment is acceptable. If documentation is not available, a serum β-HCG must be collected and sent to the local Laboratory.
Blood for Hematology, Coagulation and Chemistry	X[d]			X		X	X	Local laboratory data are used for inclusion/exclusion laboratory test.

Study Period	**Screening**	**Intervention**					**Post-treatment**	**Notes**
Visit Number/Title	1 Screening	2 Randomization	**3**	**4**	**5**	6 (EOT)	7 (TOC)	Visit 1 and Visit 2 can be done on the same day. If treatment ends before Day 14, then will go to the Visit 6 directly for EOT visit.
Scheduled Hour and Day:	≤ 24 hours prior to randomization	Day 1	Day 2	Day 3	Day 4-13	Day 14 /EOT/Early Discontinuation visit	Day 28	
Scheduling Window:		-	-	-	-	+24 hrs	±2 days	
Blood for Assessment of Creatinine and Creatinine Clearance (CrCL)	X[d]	X	X	X	X[a]	X[a]	X[a]	Local laboratory is used for assessment of Creatinine; On V1,V4,V6 and V7, perform if creatinine assessment not already done as part of 'blood for chemistry' assessment.
Urine for Urinalysis	X[d]			X[a]		X[a]	X[a]	When clinically indicated at visit 4,6 and 7. Local laboratory is used for Urinalysis.
Culture for sample of infection site and determination of pathogen	X[b, d]	X[b]	X[a]	X[a]	X[a]	X[a]	X[a]	Local microbiological laboratory will be used for culture of infection site specimen and determination of pathogen per local standards. Any suspected causative bacterial pathogen from the local microbiological laboratory culture must be isolated and available for submission to the Central Microbiology Reference Laboratory. Suspected causative bacterial pathogens should also be stored at the local microbiology laboratory for future testing if applicable.

Study Period	**Screening**	**Intervention**					**Post-treatment**	**Notes**
Visit Number/Title	1 Screening	2 Randomization	**3**	**4**	**5**	6 (EOT)	7 (TOC)	Visit 1 and Visit 2 can be done on the same day. If treatment ends before Day 14, then will go to the Visit 6 directly for EOT visit.
Scheduled Hour and Day:	≤ 24 hours prior to randomization	Day 1	Day 2	Day 3	Day 4-13	Day 14 /EOT/Early Discontinuation visit	Day 28	
Scheduling Window:		-	-	-	-	+24 hrs	±2 days	
Culture for blood sample and determination of pathogen[c]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	

a. When clinically indicated, the assessments with footnote "a" in the table must be performed.

b. Sample collection should be done at initial operative intervention. For subjects who are enrolled after surgery, collection of an intrabdominal specimen is mandatory for participants who are failures of a previous antibiotic regimen.

c. Culture for blood sample at screening is conducted as clinically indicated in participants with 1) hospital-acquired infections; 2) for those who have failed prior antibacterial therapy; or 3) who have signs of severe sepsis as assessed by the investigator.
In addition, if signs of sepsis appear or the subject is assessed as a treatment failure at any time on study (including EOT, TOC visit), a blood culture should be taken. At each blood culture collection, two sets (from two separate blood draws) of blood cultures (each set consisting of an aerobic and an anaerobic bottle) are collected. Blood culture is conducted at appropriate frequency until negative.
Local microbiological laboratory will be used for culture for blood sample and determination of pathogen per local standards. Any suspected causative bacterial pathogen from the local microbiological laboratory culture must be isolated and available for submission to the Central Microbiology Reference Laboratory. Suspected causative bacterial pathogens should also be stored at the local microbiology laboratory if possible for future testing if applicable.

d. Assessments performed prior to signing the informed consent may be used if collected during the routine care of the patient, as long as they were conducted within 24 hours prior to randomization.

2 INTRODUCTION

2.1 Study Rationale

This study is designed to demonstrate the non-inferiority of ceftolozane/tazobactam (1500 mg q8h) plus metronidazole (500 mg q8h) compared to meropenem (1000 mg, q8h) plus placebo, with respect to clinical response rate in order to support the market authorization of ceftolozane/tazobactam in China. Ceftolozane/tazobactam has been approved in US and EU for the treatment of cIAI (used in combination with metronidazole), and cUTI including pyelonephritis. The prior global cIAI Phase 2 and 3 studies were conducted outside of China; hence there is a need for an additional study in China for this indication.

Gram-negative pathogens, including ESBL producing organisms, are important causes of cIAI. The most commonly isolated pathogens in cIAI are *Escherichia coli.*, other Enterobacteriaceae, *Pseudomonas spp.* and *Bacteroides fragilis*. These infections are typically polymicrobial, also involving anaerobes such as *Bacteroides fragilis*. The spectrum of activity of ceftolozane/tazobactam plus metronidazole supports its use in treatment of pathogens commonly isolated in cIAI.

The safety and efficacy of ceftolozane/tazobactam plus metronidazole for the treatment of cIAI was demonstrated in 2 large, identical, multicenter, randomized, double-blind, active-controlled Phase 3 studies (CXA-cIAI-10-08 and CXA-cIAI-10-09). Ceftolozane/tazobactam plus metronidazole demonstrated non-inferiority to meropenem, a standard of care for the treatment of cIAIs [Solomkin, J. S., et al 2010].

As described previously, ceftolozane/tazobactam is active against the most common infecting pathogens encountered in cIAIs, and the efficacy and safety of ceftolozane/tazobactam in participants with cIAI was demonstrated in global, active-controlled Phase 3 studies. Based on the efficacy and safety of ceftolozane/tazobactam demonstrated in the global Phase 3 studies, it is considered appropriate to conduct a Phase 3 cIAI study in the Chinese patient population, to evaluate ceftolozane/tazobactam in the Chinese patient population since China did not participate in the global studies.

To ensure that there is comparability between the Chinese participants in this study and the non-Chinese participants in the global studies with respect to the safety and efficacy of ceftolozane/tazobactam, as done in Japan cIAI study (MK-7625A-013), the proportion of participants with moderate renal insufficiency (CrCL 30 to ≤ 50 mL/min) will be capped at 15% in this study. In a subgroup analysis of Phase 3 cIAI studies (CXA-cIAI-10-08 and CXA-cIAI-10-09), clinical response rates were lower in participants with baseline creatinine clearance (CrCL) of 30 to ≤ 50 mL/min (47.8%, 11/23 participants) compared to those with CrCL >50 mL/min (85.2%, 312/366 participants). A similar trend was also seen in the cUTI studies. Participants with moderate renal insufficiency in the global study had somewhat worse baseline health, compared to the rest of the participant population, and required dose adjustment of ceftolozane/tazobactam. However, in the Japan cIAI study, the clinical response rate in the CrCL ≤50 mL/min subgroup (88.9%, 8/9) was slightly lower than CrCL >50 mL/min subgroup (92.4%, 73/79). Therefore, the enrollment of the participants with CrCL (30 to ≤ 50 mL/min) is limited up to approximately 15% (40 participants) of the

total enrollment in this study in order toachieve a similar proportion of these participants as the global studies and to collect more data in Chinese participants with moderate renal insufficiency.

In the cIAI studies (CXA-cIAI-10-08 and CXA-cIAI-10-09), approximately 50% of ITT and CE participants had a primary focus of infection in the appendix, compared to a maximum of 30% recommended in the Addendum to Guideline CPMP/EWP/558/95 Rev 2 and a maximum of 50% recommended in the FDA Guidance for Industry (Complicated Intra-Abdominal Infections: Developing Drugs for Treatment, 2018). Considering epidemiology and clinical practice in China, the number of participants with localized complicated appendicitis will be limited to approximately 50% (134 participants) of the randomized population.

In addition to the results of this study, the data from the prior global studies and the Japan study as described above may be utilized to support China filing for this indication.

2.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on ceftolozane/tazobactam.

2.2.1 Pharmaceutical and Therapeutic Background

Ceftolozane/tazobactam is a fixed-dose combination of a novel antipseudomonal cephalosporin (ceftolozane) and a well-established β-lactamase inhibitor (BLI), with potent in vitro activity against most extended spectrum β-lactamase (ESBL)–producing Enterobacteriaceae and drug-resistant *Pseudomonas aeruginosa*.

Ceftolozane shares the basic chemical and biological attributes and mechanism of action with other β-lactam antibiotics. The primary mechanism of action is inhibition of the transpeptidation step of bacterial peptidoglycan biosynthesis by inactivation of penicillin binding proteins (PBPs). Ceftolozane is a member of the cephalosporin class of antibiotics, which are well characterized in terms of their safety, efficacy, and general antimicrobial profile. Cephalosporin antibiotics have been widely used in clinical practice for many years for their broad antibacterial spectrum, bactericidal activity, and excellent safety profile. A number of third and fourth generation parenteral cephalosporin antibiotics continue to be widely used (e.g., ceftriaxone, cefepime, and ceftazidime), although expanding resistance erodes their reliability. Ceftolozane exhibits time-dependent killing activity against various gram-negative organisms, including drug-resistant *Pseudomonas aeruginosa.* Ceftolozane has been shown to be potent against strains of *Pseudomonas aeruginosa* that are resistant to carbapenems, cephalosporins, fluoroquinolones, and/or aminoglycosides, including the majority of multiple drug-resistant (MDR) isolates. Like most cephalosporins, ceftolozane itself is poorly active against enterococci, ESBL-producing Enterobacteriaceae, and gram-negative anaerobes.

Tazobactam is a potent inhibitor of chromosomal- and plasmid-mediated bacterial class A and some class C β-lactamases that, by binding to the active site of these enzymes, protects ceftolozane from hydrolysis, broadening its spectrum to include most extended-spectrum β-lactamase (ESBL) -producing *Escherichia coli.*, *Klebsiella pneumoniae*, and other Enterobacteriaceae, as well as some important anaerobic pathogens (i.e., *Bacteroides fragilis*).

Ceftolozane/tazobactam does not adequately cover some pathogens implicated in cIAIs, such as gram-positive pathogens (enterococci*, Staphylococcus aureus*), and anaerobes other than *Bacteroides fragilis.*

Epidemiology and Clinical Manifestations of Complicated Intra -Abdominal Infection

Complicated intra-abdominal infection (cIAI) encompasses a wide variety of serious infections ranging from appendiceal abscesses to more severe conditions such as intestinal perforation with diffuse fecal peritonitis. In cIAI, the infectious process proceeds beyond the organ that is the source of the infection, and causes either localized peritonitis, also referred to as abdominal abscess, or diffuse peritonitis, depending on the ability of the host to contain the process within a part of the abdominal cavity. Patients with intra-abdominal infection typically present with rapid-onset abdominal pain and symptoms of gastrointestinal dysfunction (loss of appetite, nausea, vomiting, bloating, and/or obstipation), with or without signs of inflammation (pain, tenderness, fever, tachycardia, and/or tachypnea). signs of inflammation (pain, tenderness, fever, tachycardia, and/or tachypnea).

Complicated IAIs, those requiring both operative intervention and antimicrobial therapy, are very common infections encountered in general surgery, and cIAIs are an important cause of morbidity and are frequently associated with a poor prognosis. According to a global epidemiological survey of bacterial pathogens in patients with cIAI (the complicated intra-abdominal infections worldwide observational study, CIAOW study) which was conducted worldwide including China [Sartelli, M., et al 2014], the overall mortality rate was 10.1%. The immediate post-operative clinical course was a significant parameter for predicting mortality: the rate of patient mortality was 54.9% among critically ill patients (patients presenting with septic shock and severe sepsis post-operatively), but the mortality rate was only 3.3% for clinically stable patients.

Although the bacteriology of cIAI depends on the anatomic origin of the infection, these infections are usually polymicrobial and involve a wide variety of gram-negative and gram-positive aerobic and anaerobic organisms. Pathogens most commonly encountered in cIAI are *Escherichia coli.*, other common Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Bacteroides fragilis*.

The threat of antimicrobial resistance is one of the major challenges associated with the antimicrobial management of cIAI. The growing emergence of multidrug-resistant bacteria and the limited availability of new antibiotics to counteract them have brought about an impending crisis with alarming implications (especially regarding gram-negative microorganisms).

The main resistance threat in intra-abdominal infections is posed by ESBL-producing Enterobacteriaceae, which are becoming increasingly common in community acquired infections [Lee, Y. R., et al 2015]. The percentage of ESBL-positive *Escherichia coli.* isolates collected from patients with IAI significantly increased from 9% in 2002 to 23% in 2011, while the number of ESBL-positive *Klebsiella pneumoniae* isolates significantly increased from 13% in 2002 to 31% in 2007. According to the CIAOW study, among the intra-operative isolates, ESBL-producing *Escherichia coli.* isolates comprised 13.7% of all *Escherichia coli.* isolates, while ESBL-positive *Klebsiella pneumoniae* isolates represented 18.6% of all *Klebsiella pneumoniae* isolates.

Based on the SMART (Study Monitoring Antimicrobial Resistance Trends) study, in a surveillance of antimicrobial susceptibility of aerobic and facultative gram-negative bacilli isolated from participants with intra-abdominal infections in China (SMART China) from 2002 to 2009 [Yang, Q., et al 2010], the most common three pathogens for cIAI are the following, *Escherichia coli. (49.2%)*, *Klebsiella pneumoniae (16.9%)*, and *Pseudomonas aeruginosa (8.4%)*, accounting for about 70% of all isolates. Among the most common Enterobacteriaceae (*Escherichia coli.* and *Klebsiella pneumoniae*), the percentage of ESBL-positive *Escherichia coli.* isolates increased from 20.8% in 2002 to 64.9% in 2009, and the percentage of ESBL –positive *Klebsiella pneumoniae* increased from 24.0% in 2002 to 46.8% in 2009. According to the data from SMART China 2011, among the gram-negative pathogens causing IAIs, *Escherichia coli.* (47.3%) was the most commonly isolated, followed by *Klebsiella pneumoniae* (17.2%), *Pseudomonas aeruginosa* (10.1%), and *Acinetobater baumannii* (8.3%). Enterobacteriaceae comprised 78.8% (1521/1929) of the total isolates. The ESBL rates among *Escherichia coli.*, *Klebsiella pneumoniae* were 68.8% and 38.1%, respectively [Zhang, H., et al 2014].

Similar results also be found in a national survey on bacterial resistance, conducted by National Health and Family Planning Committee (Former Ministry of Health), the IAI data in 2008 indicated that the most common three isolates are *Escherichia coli. (23%), Feces Enterococcus (7.6%) and Pseudomonas aeruginosa (7.3%)*, and ESBL positive for *Escherichia coli.* and *Klebsiella pneumoniae* are 47.1% and 35.5% [Qiao-juan, H., et al 2010].

Treatment of Complicated Intra -Abdominal Infection

While cIAI is an important cause of morbidity and frequently associated with a poor prognosis, an early diagnosis, followed by adequate source control to stop ongoing contamination and restore anatomical structures and physiological function, as well as prompt initiation of appropriate empirical therapy, can limit the associated mortality.

Surgery is the most important therapeutic recourse for controlling IAI. The choice of the procedure depends on the anatomical source of infection, on the degree of peritoneal inflammation, on the generalized septic response and on the patient's general conditions.

Antimicrobial therapy plays an integral role in the management of cIAI. Empiric antibiotic therapy should account for the most frequently isolated microorganisms as well as local trends of antibiotic resistance.

In general, primary peritonitis is typically mono-microbial (e. g., due to streptococci, *Escherichia coli.*, staphylococci), whereas secondary and tertiary peritonitis are polymicrobial mixtures of aerobic and anaerobic bacteria, and occasionally fungi in case of tertiary peritonitis). In community-acquired secondary peritonitis, gram-positive and gram-negative and aerobic organisms often are implicated in infections derived from the stomach, duodenum, biliary system, and proximal small bowel. On the other hand, in hospital-acquired peritonitis, nosocomial isolates particular to the site of previous surgery and to the specific hospital and unit may determine which organisms are responsible.

For treatment of cIAI, clinical guidelines including diagnosis and management have already been established in the United States and Europe. Empiric treatment is suggested by US IDSA guideline and recommendations for treatment modification are based upon local microbiological findings. The treatment with penicillins, cephalosporins, carbapenems, monobactams, and new quinolones with or without metronidazole are recommended under different situations [Solomkin, J. S., et al 2010].

A cIAI clinical guideline is not available in China. To cover the most common pathogens in cIAI(i.e. Enterobacteriaceae and anaerobes), referring to US/EU guidelines[Solomkin, J. S., et al 2010], the current treatment options in China clinical practice include anti-pseudomonal BL/BLI combinations (piperacillin/tazobactam, cefoperazone/sulbactam), fluoroquinolones, carbapenems (imipenem-cilastatin and meropenem), and 3rd or 4th generation cephalosporins ± metronidazole.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Pre-clinical Studies

Ceftolozane/tazobactam has been well characterized in a comprehensive series of in vitro and in vivo nonclinical studies.

Ceftolozane has excellent in vitro activity (more potent than other cephalosporins) against *Pseudomonas aeruginosa*. Ceftolozane also displays potent antibacterial activity against common gram-negative and selected gram-positive organisms, including pathogens involved in respiratory and other community-acquired and nosocomial infections, such as streptococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, the majority of pathogenic enteric bacilli, and selected gram-positive anaerobic species. Ceftolozane has proven to be highly efficacious in various animal models of infection caused by either gram-positive or gramnegative bacteria, including drug-resistant strains of *Pseudomonas aeruginosa.*

Ceftolozane and tazobactam (from historical data in combination with piperacillin) each displays an excellent safety profile in animals when tested individually or in combination. In studies of ceftolozane alone, the no-observed-adverse-effect level for both rats and dogs was considered to be 300 mg/kg/day. Intravenous (IV) toxicity studies of up to 6 months' duration have been performed with tazobactam alone and in combination with piperacillin in rats and dogs. Tazobactam appears to be very well-tolerated, with no drug-related mortalities or serious clinical abnormalities. The potential target organs identified in these studies were the hematological, hepatic, and GI systems; however, only relatively minor changes were

observed in each of these organ systems. The combination of ceftolozane and tazobactam did not increase the toxicity of the individual compounds in rats after 4 weeks of repeated dosing. The combination of ceftolozane and tazobactam did not alter the PK profile of the individual compounds in a dog study.

Refer to the Investigator's Brochure (IB) for additional information on the nonclinical experience with ceftolozane/tazobactam.

2.2.2.2 Clinical Studies

To date, MK-7625A has been evaluated in 10 completed Phase 1 studies (CXA-201-01, CXA-MD-11-07, CXA-QT-10-02, CXA-ELF-10-03, CXA-DDI-12-10, CXA-201-02, CXA-REN-11-01 and CXA-EB-13-05, CXA-ICU-14-01, CXA-PEDS-13-08), 1 completed Phase 2 study (CXA-IAI-10-01), 5 completed global Phase 3 studies (CXA-cUTI-10-04, CXA-cUTI-10-05, CXA-cIAI-10-08 [MK-7625A-003], CXA-cIAI-10-09 [MK-7625A-004] and CXA-NP-11-04 [MK-7625A-008]) and two local Phase 3 Japanese studies (MK-7625A-013 and MK-7625A-014). Healthy young participants as well as participants with varying degrees of renal insufficiency have been studied, including participants with end stage renal disease (ESRD) on hemodialysis. Of note, MK-7625A-008 evaluated a higher dosing regimen of 3000 mg ceftolozane/tazobactam every 8 hours for 8-14 days for the treatment of nosocomial pneumonia.

Additional details of the Phase 1 studies and the Phase 2/3 studies involving cIAI are provided below. Refer to the Investigator's Brochure for additional information.

Phase 1 studies

Phase 1 studies show that ceftolozane exposure (Cmax and AUC) was approximately dose-proportional when administered IV over a 1-hour period to healthy volunteers with normal renal function following single doses ranging from 250 mg to 3000 mg and multiple (10-day) doses of 500 mg to 2000 mg every 8 hours and 1500 mg every 12 hours. The PK parameters for ceftolozane/tazobactam were similar following single and multiple doses, given alone or coadministered, demonstrating lack of accumulation or PK interaction. Ceftolozane elimination half-life (t½) was independent of dose and ranged from approximately 2 to 3 hours with no observed accumulation with 8 hourly dosing, thus supporting 3 times daily administration. The plasma protein binding of ceftolozane in humans ranges from approximately 16% to 21%; plasma protein binding for tazobactam is approximately 30%. Ceftolozane is eliminated in the urine as unchanged parent drug and thus does not appear to be metabolized to any appreciable extent. The beta-lactam ring of tazobactam is hydrolyzed to form the pharmacologically inactive tazobactam metabolite M1. Ceftolozane and the tazobactam metabolite M1 are eliminated by the kidneys. Following administration of a single ceftolozane/tazobactam 1500 mg intravenous dose to healthy male adults, greater than 95% of ceftolozane was excreted in the urine as unchanged parent drug. More than 80% of tazobactam was excreted as the parent compound with the remainder excreted as the tazobactam M1 metabolite. Ceftolozane is eliminated by the kidney via glomerular filtration. The ceftolozane dose normalized geometric mean AUC increased up to 1.26-fold, 2.5-fold, and 5-fold in participants with mild, moderate, and severe renal impairment, respectively,

compared to healthy participants with normal renal function. The respective tazobactam dose normalized geometric mean AUC increased approximately up to 1.3-fold, 2-fold, and 4-fold. The pharmacokinetics of ceftolozane/tazobactam is dose independent and similar between Japanese, Chinese and Caucasian healthy participants. Ceftolozane/tazobactam was safe and well-tolerated overall.

Phase 2 study in participants with cIAI (CXA-cIAI-10-01)

Study CXA-IAI-10-01 evaluated the comparative efficacy and safety study of ceftolozane/tazobactam (1500 mg every 8 hours) plus metronidazole versus meropenem (1000 mg every 8 hours) in adult participants with cIAI. The primary objective was to determine the clinical response 7 to 14 days after a 4- to 7-day treatment regimen in hospitalized participants with cIAI.

Ceftolozane/tazobactam plus metronidazole was therapeutically effective, and its activity was comparable to meropenem. Clinical cure rates in the ME population were 88.7% (47 of 53 participants) and 95.8% (23 of 24 participants) in the ceftolozane/tazobactam and meropenem treatment groups, respectively. Microbiological success rates in the ME population were 90.6% and 95.8% for participants in the ceftolozane/tazobactam and meropenem groups, respectively. Clinical curerates were similar for low-risk and high-risk participants, including the elderly, those with elevated APACHE II scores, those with failure of prior therapy, and participants with decreased renal function. Ceftolozane/tazobactam plus metronidazole was well tolerated and generally safe in this study. A similar proportion of participants in the ceftolozane/tazobactam plus metronidazole (41 of 82 participants, 50%) and meropenem (19 of 39 participants, 48.8%) groups experienced at least one AE. The incidence of SAEs was higher in the ceftolozane/tazobactam plus metronidazole group (14 participants, 17.1%) compared to the meropenem group (2 participants, 5.1%). All SAEs were reported in 1 participant each and all were assessed as unrelated to study treatment. The most common post-baseline shifts in clinical laboratory parameters in both treatment groups were elevated liver enzymes (GGT, AST, and ALT); which were consistent with known experience with β-lactam therapy. Details are in the investigator brochure.

Phase 3 study in participants with cIAI (CXA-cIAI-10-08 and CXA-cIAI-10-09)

Two large, identical, global, multicenter, randomized, double-blind, active-controlled Phase 3 studies were initiated in participants with cIAI (CXA-cIAI-10-08 and CXA-cIAI-10-09). The data for these 2 studies were prospectively pooled to form a single adequately powered Phase 3 dataset, reported in a single clinical study report.

Adult participants with a diagnosis of cIAI requiring surgical intervention were randomly assigned in a 1:1 ratio to receive ceftolozane/tazobactam (1500 mg IV every 8 hours) plus metronidazole (500 mg IV every 8 hours) or meropenem (1000 mg IV every 8 hours) plus placebo (IV every 8 hours) for 4 to 10 days. Participants were stratified at randomization by primary site of infection (bowel versus other site of IAI). A total of 970 participants were included in the ITT population, of which 476 participants were randomized to receive ceftolozane/tazobactam plus metronidazole and 494 participants randomized to receive

meropenem. 472 and 485 participants received at least 1 dose of ceftolozane/tazobactam plus metronidazole and meropenem plus placebo, respectively.

In both the US FDA and EMA analyses, ceftolozane/tazobactam plus metronidazole demonstrated noninferiority compared to meropenem for the primary and key secondary efficacy variables in the treatment of adult participants with cIAI [Solomkin, J., et al 2015]. Clinical cure rates at the TOC visit in the primary efficacy analysis population (MITT) were 83.0% (323/389) and 87.3% (364/417) for ceftolozane/tazobactam plus metronidazole and meropenem plus placebo, respectively. Clinical cure rates at the TOC visit in the CE population were 94.1% (353/375) and 94.0% (375/399) for ceftolozane/tazobactam plus metronidazole and meropenem plus placebo, respectively. Clinical cure rates the TOC visit in the ITT population were 83.6% (407/487) and 86.2% (436/506) for ceftolozane/tazobactam plus metronidazole and meropenem plus placebo, respectively. Microbiological response rate at the TOC visit in MITT population were 85.3% (332/389) and 88.7% (370/417) for ceftolozane/tazobactam plus metronidazole and meropenem plus placebo, respectively. Microbiological response rate at the TOC visit in MITT population were 85.3% (332/389) and 88.7% (370/417) for ceftolozane/tazobactam plus metronidazole and meropenem plus placebo, respectively. Additionally, ceftolozane/tazobactam plus metronidazole demonstrated high clinical cure rates in participants with common intra-abdominal pathogens including *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus salivarius*.

Ceftolozane/tazobactam plus metronidazole was well tolerated and generally safe in this study. The proportion of participants who had one or more AEs was similar in both treatment groups [44.0 % (212/482) for ceftolozane/tazobactam with metronidazole, 42.7% (212/497) for meropenem plus placebo]. The proportion of participants who had one or more SAEs was comparable in both treatment groups [2.7% (13/482) for ceftolozane/tazobactam with metronidazole, 2.2% (11/497) for meropenem plus placebo]. The proportion of participants who had AEs that led to death was comparable in both treatment groups [2.3% (11/482) for ceftolozane/tazobactam with metronidazole, 1.6% (8/497) for meropenem plus placebo].

The most common intra-abdominal gram-negative aerobic baseline pathogens were *Escherichia coli., Klebsiella pneumoniae, and Pseudomonas aeruginosa*, in addition to other pathogens such as *Bacteroides fragilis* and *Streptococcus spp*., with approximately 70% of participants having a polymicrobial infection. In the cIAI study, there was no emergence of decreased susceptibility or resistance in either treatment arm.

Phase 3 study in Japanese participants with cIAI (MK-7625A-013)

MK-7625A-013 was a multicenter, open-label, noncomparative Phase 3 study in Japanese participants with cIAI. Adult participants received ceftolozane/tazobactam 1500 mg (1000 mg of ceftolozane and 500 mg of tazobactam) plus metronidazole 500 mg IV for 1 hour every 8 hours for 4 to 14 days. The primary efficacy endpoint was the clinical response rate at TOC in the CE population and was defined in the same way as in CXA-cIAI-10-08/09.

A total of 100 participants were enrolled, 98 of whom completed the study. Ninety- six participants completed the study medication. For the primary endpoint, ceftolozane/tazobactam demonstrated a clinical response rate [95% CI] at TOC in the CE population of 92.0% (81/88 participants) [84.3, 96.7], which was similar to that observed in CXA-cIAI-10-08/09.

High response rates were also observed for the key secondary endpoints. The clinical response rates [95% CI] at EOT and LFU visits in the CE population were 94.6% (87/92 participants) [87.8, 98.2] and 90.6% (77/85 participants) [82.3, 95.8], respectively.

The microbiological response rates per-subject [95% CI] at EOT and TOC visits in the expanded microbiologically evaluable population (EME) were 93.8% (61/65 participants) [85.0, 98.3] and 90.2% (55/61 participants) [79.8, 96.3], respectively.

Against the most common baseline-infecting pathogens, microbiological response rates [95% CI] at the TOC visit were 90.2% (37/41 participants) [76.9, 97.3] for *Escherichia coli.*, 91.7% (11/12 participants) [61.5, 99.8] for *Klebsiella pneumoniae*, 100.0% (11/11 participants) [71.5, 100.0] for *Streptococcus anginosus*, 90.0% (9/10 participants) [55.5, 99.7] for *Streptococcus constellatus* and 95.2% (20/21 participants) [76.2, 99.9] for *Bacteroides fragilis*.

2.2.3 Ongoing Clinical Studies

As date of 15Nov2019, there are 2 ongoing clinical studies with ceftolozane/tazobactam: a Phase 2 study (MK-7625A-034) in pediatric participants with cUTI, and a Phase 2 study (MK-7625A-035) in pediatric participants with cIAI. A Phase 1 study (MK-7625A-036) in pediatric participants with nosocomial pneumonia is planned. Additional details may be found in the accompanying Investigators Brochure (IB).

2.2.4 Information on Other Study-related Therapy

Intravenous metronidazole will be used in participants who are randomized to ceftolozane/ tazobactam in this study. In order to maintain study blind, a placebo will be administered to participants randomized to meropenem. Metronidazole and placebo will be infused following ceftolozane/tazobactam and meropenem, respectively. An appropriate surgical intervention for target diseases will be done for all participants based on the investigators' decision, as inclusion in this study requires surgical intervention (e.g., laparotomy, laparoscopic surgery, or percutaneous draining of an abscess) within 24 hours of (before or after) the first dose of ceftolozane/tazobactam.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The following objectives and endpoints will be evaluated in adult participants diagnosed with complicated intra-abdominal infection (cIAI).

Objectives	Endpoints
Primary	
• **Objectives:** To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to clinical response at the test of cure (TOC) visit for participants diagnosed with cIAI in the clinically evaluable (CE) population. **Hypothesis:** Ceftolozane/tazobactam plus metronizazole is non-inferior to meropenem in participants with cIAI, as measured by the clinical response rate at TOC visit in the CE population.	• Clinical response: A favorable clinical response is clinical cure (see Section 8.2.1).
Secondary	

• Objective: To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to clinical response for participants diagnosed with cIAI.
  • Clinical response at the TOC visit in the intent-to-treat (ITT) population
  • Clinical response at the end of therapy (EOT) visit in the ITT and CE population
	• Clinical response

Objectives	Endpoints

• Objective: To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to microbiological response for participants diagnosed with cIAI
  • Per-subject microbiological response at the TOC visit in the expanded microbiologically evaluable (EME) population
  • Per-pathogen microbiological response at the TOC visit in the EME population
	• Per-subject microbiological response: For a favorable overall microbiological response (i.e., eradication or presumed eradication), each baseline pathogen for the participant must have a favorable microbiological outcome (see Section 8.2.2).
	• Per-pathogen microbiological response: A favorable microbiological responses include “eradication” or “presumed eradication” (see Section 8.2.2).

• Objective: To evaluate the safety and tolerability of ceftolozane/tazobactam plus metronizazole in participants diagnosed with cIAI.	• Adverse events (AEs) • Study treatment discountinuation due to AE
Exploratory	

• Objective: To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to clinical response for participants diagnosed with cIAI.
  • Clinical response at TOC visit in the microbiological intent-to-treat (MITT) population and microbiologically evaluable (ME) population
  • Clinical response at EOT visit in the MITT population
	• Clinical response

Objectives	Endpoints

• Objective: To evaluate the efficacy of ceftolozane/tazobactam plus metronizazole versus meropenem with respect to microbiological response for participants diagnosed with cIAI.
  • Per-subject microbiological response at the TOC visit in the ME and MITT population
  • Per-subject microbiological response at the EOT visit in the ME, EME and MITT population
  • Per-pathogen microbiological response at the TOC visit in the ME and MITT population
  • Per-pathogen microbiological response at the EOT visit in the ME, EME and MITT population
	• Per-subject microbiological response
	• Per-pathogen microbiological response

TOC = test of cure; EOT = end of therapy; CE = clinically evaluable; ITT = intent-to-treat; MITT = microbiological intent-to-treat; ME= microbiologically evaluable; EME = expanded ME

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active-controlled, multicenter, double-blind study of ceftolozane/ tazobactam intravenous IV infusion (1500 mg q8h) plus metronidazole (500 mg q8h) IV infusion vs. meropenem IV (1000 mg q8h) plus placebo (IV saline q8h) in participants with complicated intra-abdominal infection (cIAI) requiring surgical intervention to be conducted in conformance with Good Clinical Practices. Administration dosage of ceftolozane/tazobactam and meropenem will be adjusted according to participant's renal function. Approximately 268 adult Chinese participants with a diagnosis of cIAI will be enrolled in this study; participants will be randomized in a 1:1 ratio to receive one of two treatment arms of the study: Treatment Group 1 (ceftolozane/tazobactam 1500 mg [ceftolozane 1000 mg/tazobactam 500 mg] plus metronidazole 500 mg) or Treatment Group 2 (meropenem 1000 mg plus placebo). After a screening (baseline period) of 24 hours or less, randomized participants in each treatment group will receive assigned treatment for 4 to 14 days. All study drugs in both treatments will be administered intravenously (IV) q8h over 60-min infusions separately. Following the completion of IV study therapy, all participants have an EOT visit within 24 hours after last dose of study drug. In addition, a TOC (Day 28, ±2 days) visit will be performed in all participants. Efficacy assessments (clinical response) will be conducted at the TOC visit, as well as EOT visit. Participants will be followed for safety until the TOC visit. All participants will remain in the study for a total of approximately 31

days at maximum. In this study, no switch from IV study therapy to an oral antibacterial therapy is allowed.

Randomization will be stratified based on anatomic site of infection (bowel [small or large] vs. other site of cIAI). Participants with appendix, stomach, or duodenum as the anatomic site of infection, will be stratified to the "other site" group during the randomization process. The number of participants with localized complicated appendicitis will be limited to approximately 50% (134 participants) of the randomized population. The enrollment of the participants with CrCL (30 to ≤ 50 mL/min) is limited up to approximately 15% (40 participants) of the total enrollment.

In order to maintain the blind, placebo for metronidazole infusions must be given to those participants assigned to meropenem treatment. Placebo for meropenem must be administered to participants in the ceftolozane/tazobactam treatment group with CrCL 30 to ≤ 50mL/min due to a dose adjustment of meropenem to maintain the study blind. In addition, the infusion frequency of placebos will be adjusted according to CrCL value to ensure double dummy nature of the study. Referring to section 8.1.8 for details.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary efficacy endpoint in this study is the clinical response rate at the TOC visit in the CE population. Based on the FDA guidance (2015) for cIAI and to conduct a comparable analysis to the global cIAI studies (CXA-cIAI-10-08 and CXA-cIAI-10-09), TOC is the primary time point for efficacy. Moreover, for the same reason, in order to estimate the efficacy at the end of treatment, EOT is set as secondary time points for efficacy.

The analysis population for primary efficacy objective of this study is the CE population as the case for the Japan cIAI study. The CE population will minimize confounding factors and its efficacy analysis is expected to reflect the study drug activity. In contrast, the MITT population that is a medically complex, more heterogenous population than the CE population due to the acuity of illness, necessity for surgical precedures, and potential of acquiring other nosocomial bacterial infections. Consistent with the above expectations, in the global adult studies[Solomkin, J., et al 2015], a higher cure rate was observed in the CE population compared to the MITT population.

The analysis population of microbiological response for sencondary efficacy objective is EME population which is more inclusive and provides a broader set of pathogen data and may reflect more of a real word setting when treated before susceptibility results. In contrast,

the ME population is more stringent and may provide a better assessment of the drug's activity, but will limit the dataset.

Additional study populations have been pre-specified to be analyzed to provide a better understanding of the robustness of the primary efficacy endpoint. The analysis populations in the secondary study objectives are similar to those of global cIAI studies (CXA-cIAI-10-08 and CXA-cIAI-10-09) and Japan cIAI study.

Refer to Table 1 for a summary favorable response by efficacy endpoint and analysis population.

Table 1 Summary of Primary, Secondary and Exploratory Efficacy Endpoints and Components of a Favorable Response

Objective	Endpoint	Timing	Favorable Response	Analysis Population	References (Section/Table)
Primary Endpoint	Clinical Response	TOC	Clinical cure	CE	Section 8.2.1/ Table 5
Secondary Endpoint	Clinical Response	TOC	Clinical cure	ITT	Section 8.2.1/ Table 5
	Clinical Response	EOT	Clinical cure	ITT and CE	Section 8.2.1 / Table 5
	Micrological response	TOC	Eradication or presumed eradication	EME	Section 8.2.2 / Table 6
Exploratory Endpoint	Clinical Response	TOC	Clinical cure	MITT and ME	Section 8.2.1/ Table 5
	Clinical Response	EOT	Clinical cure	MITT	Section 8.2.1/ Table 5
	Micrological response	TOC	Eradication or presumed eradication	ME and MITT	Section 8.2.2 / Table 6
	Microbiological Response	EOT	Eradication or presumed eradication	ME, EME and MITT	Section 8.2.2 / Table 6
TOC = test of cure; EOT = end of therapy; CE = clinically evaluable; ITT = intent-to-treat; MITT = microbiological intent-to-treat; ME= microbiologically evaluable; EME=expanded microbiologically evaluable.					

4.2.1.2 Safety Endpoints

In support of the secondary objective to evaluate the safety and tolerability profile of ceftolozane/tazobactam, the safety and tolerability of ceftolozane/tazobactam (as well as the safety of the comparator, meropenem) will be assessed by clinical evaluation of adverse events and inspection of other study parameters including vital signs, physical examinations, and standard laboratory safety tests at time points specified in the SoA. Participants may be asked to return for unscheduled visits in order to perform additional safety monitoring.

4.2.2 Rationale for the Use of Concomitant/Comparator/Placebo

Metronidazole will be used in combination for all participants enrolled into the ceftolozane/ tazobactam arm of this study. Ceftolozane/tazobactam demonstrates activity against the major pathogens implicated in cIAIs such as gram-negative bacteria including Enterobacteriaceae including *Escherichia coli.*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, some of gram-positive bacteria such as *streptococci spp.*, and the anaerobe *Bacteroides fragilis*. Ceftolozane/tazobactam has limited activity against other bacteroides species beyond *Bacteroides fragilis* are major pathogens in IAIs necessitating the need for an antibacterial agent with activity against a range of anaerobic organisms. Metronidazole, a limited-spectrum, anaerobe-specific antibiotic, is commonly used in the treatment of cIAI in combination with a cephalosporin, and its use is recommended in the evidence-based guidelines for the treatment of cIAI at 500 mg every 8 hours[Solomkin, J. S., et al 2010]. Metronidazole is approved and marketed for the treatment of anaerobe infection in China and overseas. Taking into consideration this background, IV metronidazole will be used concomitantly in this study in order to appropriately treat the target pathogens associated with cIAIs. No changes to the metronidazole dose are required for renal insufficiency.

In China tertiary hospitals, carbapenems (e.g. imipenem/cilastatin, meropenem) are most widely used antibiotic for treating cIAI. Meropenem is indicated for the treatment of cIAI in the approved China label and was chosen as active comparator in the global pivotal studies [Solomkin, J., et al 2015] as well. Meropenem will be used in this study as the active comparator. Meropenem will be administered intravenously 1000 mg every 8 hours when CrCL is > 50 mL/min and 1000 mg every 12 hours when CrCL is 30 to ≤ 50 mL/min according to the approved label in China.

Since Enterococcus is one of the common pathogens in cIAI, in case an infection with MRSA or Enterococcus is suspected, antibiotics with gram-positive coverage such as vancomycin, teicoplanin, linezolid and daptomycin are allowed in the study.

This study is a double-blinded design. In order to maintain the blind, a placebo will be used in this study. After randomization, all eligible participants will be randomized to Treatment Group 1 (ceftolozane/tazobactam plus metronidazole) or Treatment Group 2 (meropenem plus placebo). Metronidazole will be administered following ceftolozane/tazobactam and placebo will be administered following meropenem, respectively.

Considering increasing resistance rate of key pathogens in cIAI e.g. *Escherichia coli.*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, especially ESBL producing strains, to widely used antibacterials in China including Carbapenems, ceftolozane/tazobactam will provide a new efficacious option in treating cIAI in clinical practice.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The dose selection of the ceftolozane component of ceftolozane/tazobactam was mainly based on the PK of ceftolozane and all known relevant pharmacokinetic/pharmacodynamics (PK/PD) principles for cephalosporins. Tazobactam, the other component of ceftolozane/tazobactam, is broadly used in China clinical practice (such as piperacillin/tazobactam). The dose of tazobactam is based on prior data which is known to be well-tolerated.

Based on the combined plasma concentration-time data from Phase 1 and 2 studies, a population PK analysis was conducted to characterize the PK of ceftolozane, and using these data, Monte Carlo simulations were conducted to evaluate the expected efficacy of different dosing regimens of ceftolozane. Like other β-lactam antibiotics, the PK/PD parameter that most closely correlates with efficacy is the time, as a percentage of the dosing interval, that the plasma concentration of ceftolozane exceeds the minimum inhibitory concentration (MIC) of the infecting organism (%T>MIC). Monte Carlo simulation analysis of clinical PK data revealed that using 30% T>MIC, an IV 1-hour infusion of 1500 mg ceftolozane/tazobactam administered every 8 hours would provide sufficient drug concentrations to cover target pathogens, with a probability of target attainment (PTA) of 100% for pathogens with an MIC of up to 8 μg/mL. According to the results from a Phase 1 study (CXA-EB-13-05), the pharmacokinetics of ceftolozane/tazobactam is dose independent and similar between Japanese, Chinese and Caucasian healthy participants.

In Phase 3 studies (CXA-cIAI-10-08 and CXA-cIAI-10-09), IV ceftolozane/tazobactam 1500 mg every 8 hours and 500 mg metronidazole demonstrated non-inferiority to IV meropenem 1000 mg every 8 hours for the treatment of cIAIs. Additionally, in Phase 3 studies of complicated urinary tract infections (cUTI) including pyelonephritis (CXA-cUTI-10-04 and CXA-cUTI-10-05), IV ceftolozane/tazobactam 1500 mg every 8 hours demonstrated non-inferiority to IV levofloxacin 750 mg once daily. In both indications, IV ceftolozane/tazobactam 1500 mg every 8 hours was generally well tolerated.

Relative to ceftolozane/tazobactam exposures in participants with normal renal function (CrCL ≥ 90 mL/min), no clinically relevant differences in exposure were observed in participants with mild renal impairment, whereas exposures increased approximately 2-fold in participants with moderate renal impairment.

Based on these results, no dose adjustment is recommended for participants with mild renal impairment (CrCL >50 to 89 mL/min). However, the ceftolozane/tazobactam dose in participants with moderate (CrCL 30 to ≤50 mL/min) is recommended to be reduced by 2-fold (i.e., 750 mg ceftolozane/tazobactam every 8 hours). Based on Monte Carlo simulation analysis a 2-fold dose reduction in participants with moderate renal impairment was predicted to produce sufficient drug concentration to cover target pathogens.

In this Chinese Phase 3 study (Protocol 015), participants with CrCL > 50 mL/min will receive ceftolozane/tazobactam 1500 mg (ceftolozane 1000 mg/ tazobactam 500 mg) every 8 hours and participants with CrCL 30 to ≤50 mL/min will receive ceftolozane/tazobactam 750 mg (ceftolozane 500 mg/tazobactam 250 mg) every 8 hours. Participants with severe renal impairment (i.e., CrCL < 30 mL/min) will not be enrolled and any participant who develops severe renal impairment during the treatment phase must be discontinued from study drug administration if already enrolled.

4.3.2 Maximum Dose/Exposure for This Study

No dose modifications are planned for this study aside from dose reductions for renal insufficiency. Therefore, the maximum dose for this study will be 1500 mg ceftolozane/tazobactam every 8 hours.

4.3.3 Rationale for Dose Interval and Study Design

The treatment period for ceftolozane/tazobactam in this China Phase 3 study (Protocol 015) will be 4-14 days. This duration was determined based on 2 global phase 3 studies (CXA-cIAI-10-08 and CXA-cIAI-10-09) and the US package insert [U.S. Prescribing Information 2016].

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male/Female Chinese participants with cIAI between the ages of 18 and 75 years (inclusive) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Have one of the following diagnoses (in which there is evidence of intraperitoneal bacterial infection) including:

    a. Cholecystitis (including gangrenous cholecystitis) with rupture, perforation, or progression of the infection beyond the gallbladder wall;

    b. Acute gastric or small intestine including duodenal perforation, only if operated on > 24 hours after perforation occurs;

    c. Traumatic perforation of the intestine (including colon), only if operated on > 12 hours after perforation occurs;

    d. Appendiceal perforation or periappendiceal abscess ;

    e. Diverticular disease with perforation or abscess;

    f. Peritonitis due to other perforated viscus or following a prior operative procedure;

        - Participants with inflammatory bowel disease or ischemic bowel disease are eligible provided there is bowel perforation(only if operated on > 24 hours after perforation occurs)

    g. Intraabdominal abscess (including liver or spleen).

2. Evidence of systemic infection including one or more of the following:

    a. Temperature (axillary) greater than 37.4°C or less than 35°C, other temperature method will be allowed based on the discussion between the sponsor and investigator (for subjects who only meet Inclusion Criterion 2a in systemic infection assessment, axillary temperature will be the required method);

    b. Elevated white blood cells (WBC >10,000/mm^3) or decreased WBC count (≤4,000 /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.

3. Requires surgical intervention (e.g., laparotomy, laparoscopic surgery, or percutaneous draining of an abscess) within 24 hours of (before or after) the first dose of study drug.

4. If participant is to be enrolled preoperatively, the participant should have radiographic evidence of gastric or bowel perforation or intra-abdominal abscess or other radiographic evidence for cIAI.

5. Subjects who failed prior antibacterial treatment for the current cIAI can be enrolled but must: (a) have a positive culture (from an intraabdominal site or blood sample) and (b) require surgical intervention. Such subjects can be enrolled before the results of the culture are known; however, if the culture is negative, study drug administration may be discontinued.

† Participants considered to have failed a previous antibiotic regimen

Should meet all of the following criteria

1) The systemic antibacterial treatment was given for at least 48 hours;
2) There are clinical plus operative findings OR clinical plus radiographic findings clearly indicating ongoing infection or worsening infection;
3) Operative intervention or re-intervention (if previous surgical procedure) is intended within 24 hours of (before or after) the first dose of study drug;

   Note: Specimens for bacterial culture and susceptibility testing are to be taken at operative intervention.Culture results do not need to be known before randomization(citing Section 8.3.12 for details).

Demographics

6. Participant is male or female.

7. Chinese participant is from 18 years to 75 years of age inclusive, at the time of signing the informed consent.

   Note: Chinese participant is defined as a person of Chinese descent, A potential participant who is of ex-China descent (e.g., Western European) descent living in China will be excluded.

Male Participants

8. Agree to use a contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 30 days (a spermatogenesis cycle) after the last dose of study medication and refrain from donating sperm during this period.

Female Participants

9. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 30 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (serum) within 48 hours before the first dose of study intervention.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 5.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

10. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has any of the following diagnoses :

    a. Simple appendicitis;

    b. Abdominal wall abscess;

    c. Small bowel obstruction or ischemic bowel disease without perforation;

    d. Spontaneous (primary) bacterial peritonitis associated with cirrhosis and chronic ascites; or

    e. Pelvic infections.

2. Has any of the following diseases:

    a. Acute suppurative cholangitis;

    b. Infected necrotizing pancreatitis;

    c. Pancreatic abscess.

3. Participant who has 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.

4. Participant who has abscess that is confirmed on imaging test but has not been or cannot be managed by surgical intervention including drainage.

5. Participant who is expected to be cured by only surgical intervention (e.g., drainage) without use of systemic antibiotic therapy.

6. Participant who has the following underlying conditions or who are at following serious conditions:

    a. Considered unlikely to survive during the study period (predicted life expectancy is < 4 weeks after randomization);

    b. Organic brain or spinal cord disease;

    c. Any rapidly-progressing disease or immediately life-threatening illness (including respiratory failure and septic shock);

    d. Immunocompromising condition, including established acquired immune deficiency syndrome (AIDS), hematological malignancy, or bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, or the administration of corticosteroids equivalent to or greater than 40 mg of prednisone per day administered continuously for more than 14 days immediately preceding randomization.

7. Participant who have a history of any hypersensitivity or allergic reaction to any beta-lactam (β-lactam) antibacterial, including cephalosporins, carbapenems, penicillins, or tazobactam, or metronidazole, or nitroimidazole derivatives;
OR if a skin test is required by local clinical regulations, the participant has a positive skin test result if no prior history of an allergic reaction to β-lactam antibacterials.

8. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that, in the opinion of the investigator, might confound the results of the study, interfere with the participant's participation for the full duration of the study, or pose additional risk in administering the study drugs to the participant.

9. A WOCBP who has a positive serum pregnancy test within 24 hours before the first dose of study intervention (see SoA and Appendix 5).

Prior/Concomitant Therapy

10. Use of systemic antibiotic therapy with known coverage of pathogens that cause IAI for more than 24 hours (e.g >1 course of a once daily antibiotic or >2 courses of q12h antibiotic) during the previous 72 hours prior to the first dose of study drug, unless there is a documented treatment failure† with such therapy.

11. For participants that are enrolled postoperatively, more than 1 dose of an active non-study antibacterial regimen administered postoperatively. For participants enrolled preoperatively, no postoperative non-study antibacterial therapy is allowed.

12. Participants who needs additional non-study systemic antibacterial therapy with gram-negative activity in addition to study drug therapy

    - Drugs with only gram-positive activity (eg, IV vancomycin, teicoplanin, linezolid and daptomycin) are allowed.

13. Participant is anticipated to be treated with Traditional Chinese Medicine or Herbal Medicine during study period.

14. Participant who received disulfiram, valproic acid or divalproex sodium within 14 days before the proposed first day of study drug or who are currently receiving probenecid.

Prior/Concurrent Clinical Study Experience

15. Is currently participating in, or has participated in, any other clinical study involving the administration of investigational or experimental medication (not licensed by regulatory agencies) at the time of the presentation or during the previous 90 days prior to screening or is anticipated to participate in such a clinical study during the course of this study.

16. Participant who has participated in a ceftolozane/tazobactam clinical study at any time in the past.

Diagnostic Assessments

17. Severe impairment of renal function (estimated CrCL <30 mL/min), or requirement for peritoneal dialysis, hemodialysis or hemofiltration, or oliguria (<20 mL/h urine output over 24 hours).

18. Has hepatic disease in the period of screening as defined by any of the following:

    a. ALT (SGPT) or AST (SGOT) > 4 x upper limit of normal (ULN);

    b. Total bilirubin > 2 x ULN, unrelated to cholecystitis;

c. Alkaline phosphatase > 4 x ULN. Participants with a value > 4 x ULN and < 5 x ULN are eligible if this value is historically stable at discretion of the investigator;

d. Acute or chronic hepatitis, liver cirrhosis, acute hepatic failure, acute decompensation of chronic hepatic failure.

19. Participant who has any of the following value in the period of screening period:

a. Hematocrit <25%;

b. Hemoglobin <8 g/dL;

c. Neutropenia with absolute neutrophil count <1,000/mm^3; OR

d. Platelet count <75,000/mm^3.

Other Exclusions

20. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

There are no dietary or activity restrictions in this study, except as medically indicated.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

Participants who have been screened but have not been previously randomized to this study may be rescreened for participation if their eligibility characteristics have changed and (a) they have not received any antibacterial therapy for the current cIAI or (b) their previous cIAI has been successfully treated and they present with signs and symptoms of a new cIAI.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies study interventions provided by the Sponsor will be packaged to support enrollment . Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Group 1	Experimental	Ceftolozane /tazobactam 1500 mg	Drug	Vial	20 mL vial Lyophilized Powder for IV Infusion	1500 mg (ceftolozane 1000 mg /tazobactam 500 mg) 750 mg† (ceftolozane 500 mg /tazobactam 250 mg)	IV Infusion	Q8h/60 min IV infusion/4-14 days	Experimental	IMP	Provided centrally by the Sponsor
Group 1	Experimental	Metronidazole 500 mg	Drug	IV bag	500 mg metronidazole and 800 mg sodium chloride in 100 mL	500 mg	IV Infusion	Q8h/ 60 min IV infusion/4-14 days	Concomitant drug	IMP	Provided centrally by the Sponsor
Group 2	Comparator	Meropenem 1000 mg	Drug	Vial	500 mg vial lyophilized powder for IV infusion	1000 mg	IV Infusion	Q8h/ 60 min IV infusion/4-14 days OR Q12h/60 min IV infusion/4-14 days[†]	Challenge Agent	IMP	Provided centrally by the Sponsor

Arm Name	Arm Type	Intervention Name	Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Group 2	Comparator	Saline	Placebo	IV bag	NA	NA	IV Infusion	Q8h/ 60 min IV infusion/4-14 days	Placebo	IMP	Provided centrally by the Sponsor

In order to maintain double dummy of the study, the placebo (saline) need to be administered in the participant with CrCL 30 to ≤50 mL/min in both arms.

Abbreviations: Q8h=every 8 hours; IV=intravenous; NA=not applicable.

† For participants with CrCL :30 to ≤ 50 mL/min.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

All IV study therapy will be reconstituted and administered according to the details provided in a separate Pharmacy Manual. An unblinded study staff (eg, pharmacist or qualified designee) at the study site will be responsible for preparing the IV study therapy for this study; this individual(s) must not be involved in any of the safety and efficacy evaluations of the study participants. Due to a visual difference in the appearance of study treatment solutions, the infusion bags will be covered with an opaque sleeve by the unblinded study staff (e.g., pharmacist or qualified designee) to ensure that other study personnel and all participants remain blinded to clinical material assignments.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to ceftolozane/tazobactam + metronidazole (Treatment Group 1) and meropenem + placebo (Treatment Group 2), respectively

6.3.2 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

- Bowel [small or large] vs. other site of cIAI

Note: Participants with appendix, stomach, or duodenum as the anatomic site of infection, will be stratified to the "other site" group during the randomization process. The number of participants with localized complicated appendicitis will be limited up to approximately 50% of the randomized population.

In addition, the randomization will also be controlled by quotas built into the IVRS/IWRS such that the enrollment of the participants with CrCL (30 to ≤ 50 mL/min) will be limited up to approximately 15% of the randomized population.

6.3.3 Blinding

A double-blinding technique will be used. Study drug will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or unblinded qualified study site personnel. Due to a visual difference in the appearance of study treatment solutions, the infusion bags will be covered with an opaque sleeve by the unblinded study staff (eg, pharmacist or qualified designee) to ensure that other study personnel and all participants remain blinded to clinical material assignments. The participant, the investigator, and Sponsor personnel or delegate(s) in this study are all blinded except for the few designated members of the unblinded study team.

In order to maintain the blind, placebo for metronidazole infusions must be given to those participants assigned to meropenem treatment. Placebo for meropenem must be administered to participants in the ceftolozane/tazobactam treatment group with CrCL 30 to ≤ 50mL/min due to a dose adjustment of meropenem to maintain the study blind. In addition, the infusion frequency of placebos will be adjusted according to CrCL value to ensure double dummy nature of the study. Referring to section 8.1.8 for details.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for ≥1 days (i.e. 3 doses if no dose adjustment made based on renal function) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination:

1. Systemic antibacterials other than study drugs: From the timing of first study drug administration to TOC visit (allow for use of systemic antibiotic in failures).

   NOTE: Vancomycin, teicoplanin, linezolid, and daptomycin are allowed if infection with MRSA or Enterococcus is suspected

2. Disulfiram, valproic acid or divalproex sodium: From 14 days before the first study drug administration to TOC visit

3. Probenecid: From the timing of first study drug administration to EOT visit

4. Systemic steroids: From the timing of first study drug administration to TOC visit. Short-term treatment with systemic (IV or oral) steroids of <1 week duration (eg, treatment for an acute asthma exacerbation or acute skin condition) is allowed. Topical steroids for the treatment of skin conditions are also allowed.

5. Systemic immunosuppressive agents: From the timing of first study drug administration to TOC visit.

6. Traditional Chinese Medicine or Herbal Medicine: From the timing of first study drug administration to EOT visit

7. Other investigational drugs: From 90 days prior to the proposed first day of study drug to TOC visit

8. Peritoneal irrigation with antibiotic-containing solutions

All prescription and over-the-counter medications (including Traditional Chinese Medicine and Herbal Medicine) other than antibacterial agents that the participant received from 7 days before the first dose of study drug and throughout the study (up to the TOC evaluation) will be documented in the eCRF.

All antibacterial agents that the participant received within 14 days before the first dose of study drug and throughout the study up to the TOC evaluation will be documented in the eCRF.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

6.6 Dose Modification (Escalation/Titration/Other)

Ceftolozane/Tazobactam

In participants with impaired renal function, it is necessary to adjust the ceftolozane/tazobactam dosage based on the grade of a renal function (creatinine clearance: CrCL). Estimate the participant's CrCL using the participant's serum creatinine value, actual body weight, and the appropriate Cockroft-Gault formula below. Careful monitoring of renal function is important, especially during the first few days following intra-abdominal surgery, as there are often fluctuations in CrCL following surgery. For participants with changing renal function (creatinine clearance is close to 50 mL/min or less), monitor CrCL at least daily and adjust the dosage of ceftolozane/ tazobactam accordingly. Elderly participants are also likely to have renal impairment, care should be taken in dose selection in this age group and it may be useful to monitor their renal function.

For serum creatinine reported in µmol/l:

$$\text{CrCL (mL/min)} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})*(0.85 \text{ if female})}{(72)(\text{serum creatinine [µmol/L] x } 0.0113)}$$

The dosage of ceftolozane/tazobactam for each creatinine clearance category is shown in Table 3.

Table 3 Administration Dosage of Ceftolozane/Tazobactam According to Renal Function

Creatinine clearance (mL/min)	Dosage of ceftolozane/tazobactam
>50	1500 mg (1000 mg ceftolozane and 500 mg tazobactam) intravenously every 8 hours [a]
30 to ≤ 50	750 mg (500 mg ceftolozane and 250 mg tazobactam) intravenously every 8 hours [a]
[a.] 2 hours window is allowed.	

Metronidazole

The dosage of metronidazole IV is administered 500 mg every 8 hours based on the package insert in China regardless of the calculation of creatinine clearance.

In order to maintain the blind, placebo for metronidazole infusions must be given at 8 and 16 hours following the first infusion (the second and fourth infusion of four times a day), to those participants assigned to meropenem treatment in order to avoid the observation that only one infusion is given.

Meropenem

Dose adjustment of meropenem in moderate renal insufficiency will require a change to q12h dosing, two 60-min dummy infusions (saline) 12 hours (± 2 hours) apart following the first infusion of the day must be administered to participants in the ceftolozane/tazobactam treatment group with CrCL 30 to ≤ 50 mL/min to maintain the study blind.

The infusion frequency of placebos will be adjusted (see examples in 8.1.8.1) according to different calculation of creatinine clearance, to ensure double dummy of the study.

The dosage of meropenem for each creatinine clearance category is shown in Table 4.

Table 4 Administration Dosage of Meropenem According to Renal Function

Creatinine clearance (mL/min)	Dosage of meropenem
>50	No dose adjustment required
30 to ≤ 50	Decrease meropenem frequency to 1000 mg IV every 12 hours [a]
[a.] 2 hours window is allowed.	

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind participants and to unmask treatment identity. In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind participants and to unmask treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

For studies using Controlled Substances, all Federal, State, Province, Country, etc. regulations must be adhered to in regard to the shipping, storage, handling and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc. laws in which the study is being conducted.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.12.3.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Severe impairment of renal function (estimated CrCL <30 mL/min), oliguria (<20 mL/h urine output over 24 hours) or requirement for hemodialysis/hemofiltration.
- Lack of efficacy: the primary or sub-investigator judges that study treatment is not efficacious (defined as lack of improvement or worsening of the baseline clinical signs and symptoms after 48 hours of study therapy).
- The index cIAI was clinically confirmed to be due to tuberculosis or of fungal, parasitic, or viral origin.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

- The participant has a confirmed positive serum pregnancy test.

  The participant's treatment assignment has been unblinded by the investigator, Merck subsidiary or through the emergency unblinding call center.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 100 mL (Appendix 2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study .If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant (all antibacterial medications taken within 14 days and other medications within 7 days before first dose of study medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study (from the first dose of study medication to TOC visit).

Since the study will enroll participants without confirmed microbiological (culture) evidence of the cIAI pathogen from intra-abdominal specimen at study entry, drugs with only gram-positive activity [e.g., daptomycin, vancomycin, linezolid] are allowed.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization OR intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.12.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Administration of study medication will be witnessed by the investigator and/or study staff.

The first dose of study intervention will be administered at the Day 1 Visit.

8.1.8.1 Timing of Dose Administration

Participants with creatinine clearance > 50 mL/min

After randomization, ceftolozane/tazobactam 1500 mg followed by metronidazole 500 mg, or meropenem 1000 mg followed by placebo will be administered intravenously every 8 hours (± 2 hours) starting on Day 1, respectively. Administration example *for participants with creatinine clearance > 50 mL/min* is shown as below.

For Participants randomized to ceftolozane/tazobactam:

8am	4pm	12am
ceftolozane/tazobactam + metronidazole	ceftolozane/tazobactam + metronidazole	ceftolozane/tazobactam + metronidazole

For Participants randomized to meropenem:

8am	4pm	12am
meropenem + placebo	meropenem + placebo	meropenem + placebo

Participants with creatinine clearance 30 to ≤50 mL/min

After randomization, the dosage of ceftolozane/ tazobactam and meropenem will be adjusted to ceftolozane/tazobactam 750 mg intravenously every 8 hours (± 2 hours) and meropenem 1000 mg intravenously every 12 hours (± 2 hours). Administration example *for participants with creatinine clearance 30 to ≤ 50 mL/min* is shown as below.

For Participants randomized to ceftolozane/tazobactam:

8am	4pm	8pm	12am
ceftolozane/tazobactam + metronidazole	ceftolozane/tazobactam + metronidazole	placebo + placebo	ceftolozane/tazobactam + metronidazole

For Participants randomized to meropenem:

8am	4pm	8pm	12am
meropenem + placebo	placebo + placebo	meropenem + placebo	placebo + placebo

Treatment duration for all participants and decision of treatment completion

Participants should receive study drug for a minimum of 4 days (unless clinical failure occurs earlier or an AE necessitating early discontinuation occurs), and end the treatment of study drug within 14 days.

After 4 days and at the discretion of the Investigator, study drug administration may be discontinued if the participant has shown signs and symptoms of clinical improvement such as:

- WBC count is 4,000 to < 10,000/mm^3;
- Maximum axillary temperature has been < 37.4 °C, for > 24 hours, without the influence of antipyretic agents, such as aspirin, acetaminophen, non-steroidal anti-inflammatory drugs, or corticosteroids; other body temperature measurements

method will be allowed as long as the same method is used for a participant throughout the study;

- Improvement of abdominal signs and symptoms manifested at study entry;
- Return of bowel function and restoration of oral/enteral intake; and
- No further antibiotic therapy is required.

Metronidazole and the saline placebo should be given for the same duration as the study drug.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the 14 days treatment should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE PARTICIPANT UNLESS NECESSARY.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the drug used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, IVRS/IWRS should be used for emergency unblinding in the event that this is required for participant safety.

8.1.11 Domiciling

This study will only enroll participants who are expected to be hospitalized during the period of study therapy and is consistent with the clinical management of cIAI infection in China. Study medications will not be admistered as outpatients.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

The primary efficacy endpoint in this study is clinical response (i.e. clinical cure rate) at TOC visit in CE population. In order to assess the efficacy at the end of treatment of ceftolozane/tazobactam, EOT is set as secondary time point for efficacy.

Different study populations have been pre-specified and to be analyzed to have better understanding the robustness of efficacy. The analysis populations in the study objectives are comparable to those of global cIAI study (CXA-cIAI-10-08 and CXA-cIAI-10-09).

8.2.1 Clinical Response

Clinical outcome assessments will be made at the EOT and TOC visits. Clinical response will be classified by the investigator as cure, failure, or indeterminate. A favorable clinical response is “clinical cure”.

Failure will be carried forward; participants who are assessed as a failure prior to the TOC visit should have “failure” recorded on the TOC outcome visit eCRF, regardless of their final outcome at that time. Participants who are assessed as a failure prior to the TOC should attend the TOC visit but will not have a clinical outcome assessment at the TOC visit.

Clinical cure, clinical failure, and indeterminate responses are defined in Table 5.

Table 5 Clinical Response Categories at the EOT and TOC Visits

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

8.2.2 Microbiological Response

Per Subject Microbiological Outcomes

An overall microbiological response will be determined by the Sponsor for each participant based on individual microbiological responses for each baseline bacterial pathogen. In order for the participant to have a favorable overall microbiological response (i.e., eradication or presumed eradication), each baseline bacterial pathogen must have a favorable microbiological outcome. If the outcome for any baseline bacterial pathogen is unfavorable, the participant will be considered an overall microbiological failure. Per participant microbiological response is assessed at both the EOT and TOC visits.

Per Pathogen Microbiological Outcomes

A microbiological response will be determined for each bacterial pathogen isolated at baseline by the Sponsor. Microbiological response categories are eradication, presumed eradication, persistence, persistence acquiring resistance, presumed persistence, and indeterminate, as defined below in Table 6. Favorable microbiological responses include "eradication" or "presumed eradication." "Persistence," "persistence acquiring resistance," and "presumed persistence" are considered unfavorable responses. Per pathogen microbiological response is assessed at both the EOT and TOC visits.

Table 6 Microbiological Outcome Categories

Outcome	**Definition**
Eradication	Absence of the baseline bacterial pathogen in a specimen appropriately obtained from the original site of infection
Presumed eradication	Absence of material to culture in a participant who is assessed as a clinical cure
Persistence	Presence of the baseline bacterial pathogen in a culture of an appropriately obtained specimen from the site of infection or surgical wound. Cultures from indwelling drains are not considered appropriate.
Persistence acquiring resistance	As above, and the baseline bacterial pathogen that was susceptible to study drug pretreatment is resistant to study drug post-treatment.
Presumed persistence	Absence of material to culture in a participant who is assessed as a clinical failure
Indeterminate	Baseline culture either not obtained or has no growth Assessment not possible Any other circumstance that makes it impossible to define the microbiological response (e.g., participant lost to follow-up)

Pathogens isolated after baseline will be assessed for the outcome of superinfection or new infection, as defined in Table 7.

The percentage of participants with superinfection or new infection will be determined.

Table 7 Emergent Infection

Outcome	**Definition**
Superinfection	Isolation of a pathogen, other than the original baseline pathogen(s), from an intraabdominal specimen taken from a participant with signs or symptoms of infection **while on study drug**
New infection	Isolation of a pathogen, other than the original baseline pathogen(s), from an intraabdominal specimen in a participant with signs or symptoms of infection **after treatment with study drug**

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard systems/evaluations.Citing the SoA and the visit requirements (Section 8.12) for details.

A full physical examination, performed at randomization includes the following assessments: general appearance, head, eyes, ears/nose/ throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated. If a physical examination was performed within 72 hours prior to screening, those results can be recorded and a repeat physical examination is not required. Any abnormal or clinically significant findings from the physical examinations must be recorded on the appropriate eCRF.

A brief directed physical examination targeted to the participant's illness and complaints will be conducted by an investigator or medically qualified designee (consistent with local requirements) in the period of study therapy at the discretion of the investigator and at TOC visit as specified in Section 1.3–SoA.

Investigators should pay special attention to clinical signs related to cIAI.

8.3.2 Vital Signs

- Axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed (other body temperature measurement methods will be allowed as long as the same measurement method is used for a participant throughout the study).

- Blood pressure and pulse measurements are recommended tobe assessed in a supine or semi-recumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.

8.3.3 Height and Weight

The participant's height and weight should be measured prior to initiation of IV study therapy during the screening.

8.3.4 Surgical wound examination

Conduct surgical wound examination at the visits specified in SoA to assess signs of infection such as skin erythema, induration, tenderness, swelling, and wound pain (superficial). If signs of infection are present, findings will be recorded and graded as mild, moderate, or severe according to the definitions provided in section 8.3.6. Warmth and fluctuance will be assessed as absent or present. The nature of any discharge (non-purulent or purulent) will also be assessed. Surgical wound examination should be conducted at the baseline visit if participant already had surgical intervention before the allocation. On each study day, surgical wound examination will be conducted by the Investigator. It is preferred that this assessment should be performed approximately at the same time each day (e.g., every morning).

8.3.5 APACHE II Score

Severity of illness in this study will be determined by APACHE II score at screening . See Appendix 8 for details regarding the calculation of this score. Results of APACHE II score calculations must be entered on the appropriate eCRF(s).

8.3.6 Abdominal symptoms and signs

Abdominal symptoms and signs will be assessed at screening and collected daily during the period of IV study therapy, end of IV study therapy (EOT) and post-treatment visit (TOC).

Thorough clinical examinations of the abdomen will be conducted. Specific findings such as abdominal pain, tenderness to palpation, rebound tenderness, guarding, or presence of ascites, will be assessed and grades as none, mild, moderate or severe according to the following definitions:

- None: sign or symptom absent
- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: sign or symptom of enough intensity to cause interference with usual activity
- Severe: sign or symptom of enough intensity to incapacitate

On each study day thereafter, each cIAI symptom will be assessed by the Investigator as unchanged, worse, or improved compared to the baseline symptom assessment.

Other pertinent findings should be recorded, including ability to tolerate oral or enteral intake and presence of ileus.

8.3.7 Radiographic examination (Ultrasound, X-ray or CT etc)

Specific radiographic examinations are not required for this study unless the participant is enrolled pre-operatively or clinically indicated. Bowel perforation or intra-abdominal abscess must be observed. Radiological examinations should only be performed as required for routine participant management. Radiologic evaluations might include plain abdominal radiograph, computerized tomography (CT) scan, ultrasound, and/or magnetic resonance imaging (MRI) scan, with or without contrast. The results of any such studies should be recorded.

Retain copies of all interventional radiological reports and diagnostic study reports for collection during monitoring visits.

Any abnormal or clinically significant findings must be recorded on the appropriate eCRF.

8.3.8 Diagnosis of target disease and site of infection

Participant must have at least one clear diagnosis of target disease as listed in the section 5.1, and also the corresponding site of infection before the randomization.

Assess and record the diagnosis of target disease, anatomic site of infection, the presence and extent of abscesses (i.e. presence or absence of a abscess, single or multiple abscess), the presence and extent of peritonitis (i.e. presence or absence of peritonitis, local or diffuse), the etiological mechanism (i.e., postoperative/hospital acquired infection, trauma, spontaneous rupture, malignancy or other) and infection history (i.e. new infection or failure of prior antibiotic therapy) at screening.

8.3.9 Record any blood or blood product transfusions

Participants with surgical intervention, record any blood or blood product transfusions in the previous 48 hours during the screen period. For the rest visits of the study, record any transfusions of blood or blood products.

8.3.10 Record summary of operative procedures and operative notes

During the trial, record summary of initial and any subsequent interventional operative procedure and operative note for complicated intra-abdominal infection (e.g laparotomy, laparoscopic surgery, or percutaneous draining of an abscess) in the eCRF and retain source records of all operative procedure notes for collection during monitoring visits. The initial interventional procedure must intend to achieve adequate source control, (i.e., all communications between the GI tract and the peritoneal cavity are closed), no necrotic intestine (or other tissue) is left, and all infected collections are drained).

8.3.11 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Local Laboratory Monitoring for Renal Function

During this study period, serum creatinine value to determine dose adjustment will be collected in local laboratory. Obtain serum creatinine value and estimate the participant's CrCL using the participant's serum creatinine value, actual body weight, and the appropriate Cockroft-Gault formula described in section 6.6 at the visit specified in SoA.

For participants with renal insufficiency or whose creatinine clearance changes during treatment with study therapy (refer to Table 3 and Table 4 in Section 6.6), the dose of study drug must be adjusted based upon the degree of renal function impairment as determined by the estimated or actual creatinine clearance.

Results of these local laboratory tests must be documented in the appropriate eCRF. Laboratory abnormalities resulting in an adverse event or dose adjustment should also be collected on the appropriate eCRF. Any clinically relevant laboratory test abnormality that emerged during study therapy and was considered by the investigator to be an adverse event or event of clinical interest should be repeated until the abnormal value has normalized, stabilized, or returned to baseline.

8.3.12 Criteria for Baseline Culture

The Investigator will collect intraabdominal specimens for culture of both aerobes and anaerobes at the time of the initial procedure. Specimens should be collected at the beginning of the interventional procedure prior to debridement, removal or disinfection of the primary site of infection. Aspirates (collected with a needle or syringe) or tissue or biopsy samples are recommended, swabs of purulent material are discouraged.

Sample collection should be done at initial operative intervention. For subjects who are enrolled after surgery, collection of an intrabdominal specimen is a mandatory requirement only for participants who failed prior antibacterial therapy .

Participants who are not failures of prior treatment (i.e., have not received prior antibacterial treatment for the current cIAI) with negative culture results from intraabdominal specimens should continue with study drug treatment and have all study procedures performed as outlined in the protocol.

Participants enrolled with failure of a prior regimen with negative culture results from intraabdominal specimens and blood sample are considered to have undocumented evidence of prior treatment failure and may discontinue study drug treatment and completed study procedures as outlined in the protocol.

Blood samples for culture will be drawn in participants with hospital-acquired infections, those who have failed prior antibacterial therapy, or who have signs of severe sepsis.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention allocation/randomization through TOC visit, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 8.

Table 8 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply wth country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Treatment failure or relapse will be captured on the clinical response pages, and only needs to be reported as an SAE if the SAE criteria are met (such as prolongation of existing hospitalization). Treatment failure includes progression, relapse, or recurrence of new symptoms or complications attributable to cIAI or a lack of resolution (persistence) or insufficient improvement in signs and symptoms of cIAI which were present at baseline.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

  *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

In this study, an overdose is defined as any dose that is more than 2 times higher than the protocol-specified dose for the patient's renal function.

No specific information is available on the treatment of overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

Not applicable.

8.9 Planned Genetic Analysis Sample Collection

Not applicable.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

8.11 Health Economics Medical Resource Utilization and Health Economics

Health Economics OR Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening (Visit 1)

Baseline (screening) assessments are to be performed as close as possible to the start of study therapy and at most within 24 hours before randomization. If a participant is enrolled and dosed pre-operatively, it is acceptable that the sample from the site of infection be obtained following the start of administration of the first dose of study drug. All potential study participants will undergo the same screening evaluations, which will include obtaining a medical history and performing clinical examinations and laboratory tests. All baseline assessment results except the results of the culture must be available before randomization and study drug administration..

8.12.2 Treatment Period (Visit 2 to Visit 6)

The treatment period for ceftolozane/tazobactam in this study should be a minimum of 4 full days to up to a maximum of 14 days. All study assessments are recommended to be performed at an approximately consistent time of day for the participant (e.g. every morning) for each calendar day.

Assessments and procedures during the study therapy will be completed at the indicated times and intervals as per Section 1.3 – SoA. The EOT visit for participants will be completed within 24 hours after the last dose of study therapy.

8.12.3 Follow-up Period (Visit 7)

Participants will be required to return to clinic at Day28+/-2days (TOC visit). If the TOC visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A randomized, active-controlled, parallel-group, multicenter, double-blind study of ceftolozane/tazobactam IV infusion (1500 mg q8h) plus metronidazole (500 mg q8h) IV infusion vs. meropenem IV (1000 mg q8h) plus placebo in Chinese participants with cIAI.
Treatment Assignment	*Randomization method*: Participants will be randomized in a 1: 1 ratio to two treatment arms of the study, Treatment 1 (ceftolozane/tazobactam + metronidazole) group or Treatment 2 (meropenem + placebo) group. Both treatments will be administered IV q8h. *Stratification method*: Randomization will be stratified by anatomic site of infection (bowel [small or large] vs. other site of cIAI). Participants with appendix, stomach, or duodenum as the anatomic site of infection, will be stratified to the "other site" group during the randomization process. *Double-dummy double-blind method*: A double-blinding technique will be used. Study drug will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or unblinded qualified study site personnel. The participant, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment administration or clinical evaluation of the participants are unaware of the group assignments
Analysis Populations	Primary Efficacy Analysis: Clinical evaluable (CE) population. Secondary Efficacy Analysis: Intent-to-treat (ITT) population, microbiological intent-to-treat (MITT) population, microbiologically evaluable (ME) population and expanded microbiologically evaluable (EME) population. Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	Clinical response at the TOC visit
Secondary Endpoints	Clinical response at the EOT visit Microbiological response (Per-subject and per-pathogen microbiological response) at the TOC visit

Statistical Methods for Key Efficacy	For the primary hypothesis (clinical response rate at the TOC visit in the CE population), Treatment 1 (ceftolozane/tazobactam + metronidazole) will be considered non-inferior to Treatment 2 (meropenem + placebo) if the lower bound of the 2-sided 95% confidence interval for the between-treatment difference in the clinical response rate (Treatment 1 minus Treatment 2) is larger than -12.5%. The two-sided 95% confidence intervals for between-treatment differences in the clinical response rate will be calculated using the stratified Miettinen and Nurminen method with the Cochran-Mantel-Haenszel (CMH) weighting. For secondary objectives, point estimates and two-sided 95% confidence intervals will be calculated using the same stratified Miettinen and Nurminen method as described above.
Statistical Methods for Key Safety Analyses	P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the unstratified Miettinen and Nurminen method.
Interim Analyses	A blinded review of the clinical response rate will be ongoing during the study. The impact of the blinded clinical response rate on the assumptions underlying the power/sample size calculation will be formally assessed by the Sponsor when approximately 75% of the planned sample size (N=201) have completed TOC visits or sooner if enrollment or event rates are occurring faster than anticipated. If the clinical response rate at the TOC visit is lower than the 90% assumed in the power calculation, consideration will be given to increasing the sample size. There are no plans to conduct a formal interim analysis of unblinded efficacy data in the study.
Multiplicity	No multiplicity adjustment is planned as there is a single comparison of 2 treatments using 1 endpoint in the primary hypothesis. Other efficacy analyses will be considered supportive and/or explanatory.
Sample Size and Power	The planned sample size is 268 participants (134 per arm). Assuming a 75% evaluability rate in the CE population, it is expected that 200 CE participants (100 participants per arm) will be included. For the clinical response rate at the TOC visit in the CE population, the study has 80% power to demonstrate that Treatment 1 (ceftolozane/tazobactam + metronidazole) is non-inferior to Treatment 2 (meropenem + placebo) using a 1-tailed alpha of 2.5%, if there is no underlying treatment difference. The power and sample size are based on the following assumptions: 1) a non-inferiority margin of -12.5%, and 2) an underlying clinical response rate of 90% in the CE population for both treatments.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study. Unblinded Sponsor personnel [ie. unblinded CRA (uCRA), unblinded data manager (uDM), unblinded clinical scientist (uCS)], will be assigned to support the oversight and monitoring of study conduct. The uCRA will ensure that unblinded monitoring activities are conducted in compliance with protocol and

regulatory requirements and the Trial Specific Site Monitoring Plan. The uDM will perform data review and reconciliation for unblinded eCRF data. The uCS will provide support and guidance on study-specific unblinded procedure-related questions, in particular, questions related to the blinded clinical supplies as well as support for the uDM on data review issues requiring consultation.

The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice/web response system (IVRS/IWRS).

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

Non-Inferiority Margin Justification:

A conservative method for estimating the treatment difference is adopted by comparison of the lower bound of the 95% CI for the antibacterial drug therapy and the upper bound of the 95% CI for placebo/no treatment. The source data were obtained from the previous pivotal studies or medical literature. An upper bound of the 95% CI of 64.9% for placebo/no treatment was directly obtained from 2015 FDA Guidance for Industry *Complicated Intra-Abdominal Infections: Developing Drugs for Treatment*. For antibacterial drug therapy, a meta-analysis for the clinical response rates was applied using study results from the two most commonly used cIAI drugs; meropenem and imipenem/cilastatin (Table 9). In this meta-analysis, a point estimate of 87.8% with a two-sided 95% CI of 84.9% and 90.8% was calculated. For consistency of analyses, the DerSimonian and Laird method using random effects was applied to both the above mentioned FDA guidance and the antibacterial drug results in Table 9.

Given an estimated treatment difference of 20.0% (84.9% minus 64.9%) and consideration of a 12.5% NI margin suggested by EMA guidance *Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 REV 2) to address indication-specific clinical data*, the non-inferiority margin is selected to be 12.5%, which represents preserving about 40% of the estimated treatment difference of 20%, as shown above.

Table 9 Clinical response rate at TOC visit

Drug	Clinical response rate at TOC n/N(%[95%CI])	Source	Note
Meropenem	364/417 87.3%[83.75, 90.15]	CXA-cIAI-10-08-09	Global study
Imipenem/cilastatin	50/55 90.9%[80.0, 97.0]	Chen et al. BMC Infectious Diseases 2010, 10:217	Chinese participants

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

A full description of the efficacy measures is provided in Section 4.2.1.1.

The primary efficacy endpoint is clinical response at the TOC visit in the CE population.

The secondary efficacy endpoints are:

(1) Clinical response at the TOC visit in the ITT population.

(2) Clinical response at the EOT visit in the ITT and CE population.

(3) Percentage of participants achieving a favorable microbiological response at the TOC visit in the EME population.

(4) Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the TOC visit in the EME population.

The exploratory efficacy endpoints are:

(1) Clinical response at the TOC visit in the MITT population and ME population.

(2) Clinical response at the EOT visit in the MITT population.

(3) Percentage of participants achieving a favorable microbiological response at the TOC visit in the ME and MITT population.

(4) Percentage of participants achieving a favorable microbiological response at the EOT visit in the ME, EME and MITT population.

(5) Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the TOC visit in the ME and MITT population.

(6) Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the EOT visit in the ME, EME and MITT population.

9.4.2 Safety Endpoints

The descriptions of safety measurements are provided in Section 4.2.1.2.

Based upon a review of adult and pediatric trial safety data, no Tier 1 AEs of clinical interest have been identified. The broad clinical and laboratory adverse event (AE) categories, consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug related and serious, discontinuation of IV study therapy due to an AE, discontinuation of IV study therapy due to a drug-related AE, and an AE leading to death will be considered Tier 2 endpoints.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The Clinically Evaluable (CE) population will serve as the primary population for the analysis of efficacy data in this study. The Intent-to-Treat (ITT), Microbiological Intent-to-treat (MITT), Microbiologically Evaluable (ME) and Expanded Microbiologically Evaluable (EME) populations will serve as secondary populations for efficacy analyses.

The ITT population will consist of all randomized participants. Participants in the ITT population will be analyzed based on the treatment they were randomized to, irrespective of what they actually received.

The MITT population will consist of all randomized participants who have a baseline bacterial pathogen known to cause cIAI, regardless of susceptibility to study drug. Participants in the MITT population will be analyzed based on the treatment they were randomized to, irrespective of what they actually received.

The CE population consists of subjects who meet the protocol definition of cIAI, who adhere to study procedures and have a clinical outcome at the TOC visit. Further specific details defining this population will be provided in the sSAP.

The CE population does not require a bacterial pathogen identified as the cause of cIAI.

The ME population is the subset of CE participants who have at least one baseline intraabdominal pathogen identified that is susceptible to study drug.

The EME population consists of all randomized participants who have cIAI as evidenced by identification of at least 1 baseline intra-abdominal pathogen, regardless of susceptibility to study drug and meet all CE population criteria.

The CE, ME, and EME populations will serve as the per-protocol analysis populations for the analysis of efficacy data in this study.

9.5.2 Safety Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received any amount of study treatment (i.e. at least one dose, including only a partial dose). Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

For the analysis of pre-specified events of interest (Tier 1 events) described above in Section 9.4.2, participants will be excluded from specific analyses if the conditions defining the event were present at randomization (Day 1).

Details on the approach to handling missing data for safety analyses are provided in Section 9.6 Statistical Methods.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size limitations, etc. Unless otherwise stated, all statistical tests will be conducted at α=0.025 (1-sided) level.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

Primary Efficacy Analysis

The primary objective is to establish non-inferiority of Treatment 1 (ceftolozane/tazobactam + metronidazole) to Treatment 2 (meropenem + placebo) with respect to clinical response rate in the CE population at TOC visit. 95% confidence intervals for between-treatment differences in the clinical response rate will be calculated using the stratified Miettinen and Nurminen (M&N) method (1985) with the Cochran-Mantel-Haenszel (CMH) weighting. The analyses will be stratified by anatomic site of infection (bowel [small or large] vs. other site of cIAI). Treatment 1 (ceftolozane/tazobactam + metronidazole) will be considered non-inferior to Treatment 2 (meropenem + placebo) if the lower bound of the 2-sided 95%

confidence interval of the between-treatment difference in clinical response rate (Treatment 1 minus Treatment 2) at TOC in the CE population is larger than -12.5%.

Secondary Efficacy Analysis

The secondary efficacy analysis will follow the same stratified M&N method described above for the primary efficacy analysis. The estimates and their two-sided 95% confidence intervals will be calculated for each secondary efficacy endpoint. The secondary efficacy objectives are estimation objectives only, so no NI testing will be applied on the secondary efficacy analysis.

Missing Values

Any participant missing an evaluation for a specific endpoint (clinical or microbiological) at any particular visit will be generally considered as being "indeterminate" for that endpoint in the ITT and MITT populations. Participants with an indeterminate clinical outcome will be considered as "Treatment Failure" in the ITT and MITT analysis populations. Participants with an indeterminate clinical outcome will be excluded from per-protocol analysis populations (CE, ME and EME). The following are exceptions to this rule:

- Participants discontinuing IV study therapy due to lack of efficacy (i.e., withdrawals with subsequent non-study antibiotic therapy or participants requiring therapy beyond 14 days) will be considered as "failures" with respect to clinical response at the time of discontinuation and all subsequent time points in all populations.

- Participants discontinuing IV study therapy due to lack of efficacy will be presumed to have persistence for the microbiological response at the time of discontinuation and all subsequent time points.

The primary and secondary endpoints, primary and secondary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 10. Since a favorable clinical response and favorable microbiological response requires a clear assessment, an assessment of "indeterminate" would be considered treatment failure in the ITT and MITT populations.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis:			
Clinical response at the TOC visit	Stratified M&N‡	CE§	DAO††
Secondary Endpoints:			
Clinical response at the TOC visit	Stratified M&N‡	ITT%	M=F‡‡
Clinical response at the EOT visit	Stratified M&N‡	ITT% CE§	M=F‡‡ DAO††
Percentage of participants achieving a favorable microbiological response at the TOC visit	Stratified M&N‡	EME#	DAO††
Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the TOC visit	Stratified M&N‡	EME#	DAO††

† Statistical models are described in further detail below:

‡ M&N is Miettinen and Nurminen method stratified by anatomic site of infection (bowel [small or large] vs. other site of cIAI).

§ The CE population consists of subjects who meet the protocol definition of cIAI, who adhere to study procedures and have a clinical outcome at the TOC visit. Further specific details defining the CE population will be provided in the sSAP.

% ITT population consists of all randomized participants.

¶ MITT population: consist of all randomized participants who have a baseline bacterial pathogen known to cause cIAI.

ME population is the subset of CE participants who have at least one baseline intraabdominal pathogen identified that is susceptible to study drug. EME population is expanded ME population.

†† DAO is data as observed, that is, participants with missing values will be excluded from the analysis.

‡‡ M=F is missing =failure

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and multiple time points is described in Section 9.7, Interim Analyses and in Section 9.8, Multiplicity.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs.

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory and vital signs are either pre-specified as “Tier-1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or adverse events of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol based upon a review of adult and pediatric trial safety data.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for differences in the proportion of participants with events (also via the M&N method (1985)).Membership in Tier 2 requires that at least 4 participants in at least one treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

Continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	None	X	X	X
Tier 2	Any AE‡		X	X
	Any Serious AE		X	X
	Any AE leading to death		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs† (incidence ≥4 of participants in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs† (incidence <4 of participants in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X

† Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.

‡ Indicates broad AE category of the number of participants reporting any adverse event.

Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment using descriptive statistics for continuous or categorical variables, as appropriate.

9.7 Interim Analyses

An internal blinded sample size re-estimation will be conducted as described in the next paragraph. There are no plans to conduct a formal interim analysis of unblinded efficacy data in the study.

Blinded review of clinical response rate at TOC visits on the CE population will be ongoing during the study. The impact of the clinical response rate on the assumptions underlying the power/sample size calculation will be formally assessed when approximately 75% (N=201) of the planned sample size (N=268) have completed TOC visits or sooner if enrollment or

event rates are occurring faster than anticipated. In consideration of having enough time for blinded sample size re-estimation as well as a stable estimate for the clinical response rate, 75% is selected as the time point for the blinded sample size assessment.

If the observed, blinded (pooled) clinical response rate is lower than the 90% assumed in the power calculation, consideration will be given to increasing the overall sample size as outlined in Table 12. If the observed clinical response rate is larger than 90%, the overall sample size will be maintained at the planned N=268 as the power for this endpoint/hypothesis will likely exceed 80%. The maximum sample size will not exceed N=408 (204 per group) regardless of the observed clinical response rate.

Blinded review of clinical response is not a true interim analysis in that it will not require a dataset freeze, unblinding, and multiplicity adjustments. The accruing database will not be officially locked for this blinded sample size re-estimation; however, all data relating to the assessment of clinical response rate will be cleaned and all queries resolved before the formal assessment of the clinical response rate. As this sample size re-estimation will be done in a blinded fashion, there is no impact on type 1 error rates.

Table 12 Sample Size Adjustments based on Interim Blinded Review of Clinical Response Rate at TOC Visit

Observed Clinical Response Rate†	Power based on Original Sample Size (N=268) (%)	Revised Sample Size‡	Percent Increase from Original Sample Size (%)
89%	77.2	294	9.7
88%	74.6	310	15.7
87%	72.2	328	22.4
86%	70.0	344	28.4
85%	67.9	360	34.3
84%	66.0	376	40.3
83%	64.0	392	47.3
82%	62.2	408	52.2

† This rate is expressed as a percent and rounded to the nearest integer value.

‡ Calculated to provide 80% power based on the observed clinical response rate and assumed evaluable rate of 75% in CE population in the power/sample size calculation.

Note: The calculation is also based on the assumptions from the sample size section, i.e. one-sided 2.5% alpha-level, no underlying treatment difference, and NI margin of -12.5%.

9.8 Multiplicity

As there is only a single primary efficacy hypothesis which is being conducted at the one-sided α=0.025 level, no multiplicity adjustment is needed for the primary efficacy analysis.

The secondary efficacy objectives are estimation objectives, are supportive in nature and have no associated hypotheses. Therefore, no multiplicity adjustment is necessary for the secondary efficacy analysis.

There will be no multiplicity adjustments applied to the safety summaries.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

This study will randomize 268 participants (134 per treatment arm) into the study and has 80% power to establish that Treatment 1 (ceftolozane/tazobactam + metronidazole) is non-inferior to Treatment 2 (meropenem + placebo) in the clinical response rate at the TOC visit in CE population at an overall one-sided, 2.5% alpha-level, if there is no underlying treatment difference. The power and sample size are based on the following assumptions: 1) an approximately 75% evaluable rate in CE population 2) a non-inferiority margin of -12.5% (Treatment 1 minus Treatment 2), and 3) an underlying clinical response rate of 90% at the TOC visit. Above assumption is based on the pivotal study CXA-cIAI-10-08-09 CSR. The non-inferiority margin is regarded as the minimum difference of clinical interest between the 2 treatments [rationale is described in Section 9.3]. The calculation is based on an asymptotic method proposed by Miettinen and Nurminen (1985) with 100 participants per group expected to be included in the analysis in CE population and is carried out using PASS by selecting the test type of likelihood score (Miettinen & Nurminen) in the Non-inferiority & superiority tests for two proportions [differences] module. The minimum criterion for success is that the lower bound of the 95% CI on the treatment difference (Treatment 1 minus Treatment 2) > -12.5%. Table 13 summarizes power calculations for the primary comparison under various assumptions.

Table 13 Power (%) Under Various Assumptions (With 268 participants (134 per arm) into the study and NI margin of -12.5%)

Underlying clinical response rate of treatment 2 at TOC visit	Underlying Treatment Difference (%) (Treatment 1 - Treatment 2)					
	2	1	0	-1	-2	-3
82%	76.9	69.9	62.2	54.3	46.4	38.7
84%	80.6	73.7	66.0	57.8	49.5	41.4
86%	84.4	77.7	70.0	61.6	52.9	44.4
88%	88.5	82.2	74.6	66.0	56.9	47.8
90%	92.6	87.2	80.0	71.4	61.9	52.0
92%	96.4	92.4	86.1	77.9	68.1	57.5
94%	99.0	96.9	92.5	85.5	76.1	65.0

Note: The power is calculated based on 100 participants per each treatment group expected to be included in the analysis in the CE population.

Another way to assess the precision of a non-inferiority study is to consider the minimum observed difference that would just meet the criterion for non-inferiority (in this case, a lower bound of the 2-sided 95% CI for the difference in clinical response rate in CE population [Treatment 1 minus Treatment 2] that is just larger than -12.5%). This minimum observed difference will decrease as the observed clinical response rate in the control group increases (Table 14). An observed clinical response rate of 90% in the treatment 2 will just meet the criterion for non-inferiority given an observed difference (Treatment 1 – Treatment 2) is not less than -3.2%, that is the observed clinical response rate in the treatment 1 is not less than 86.8%. An observed clinical response rate of 86% in the treatment 2 will just meet the criterion for non-inferiority given an observed difference (Treatment 1 – Treatment 2) is not less than -2.3%, that is the observed clinical response rate in the treatment 1 is not less than 83.7%. Above calculation is carried out using PASS by selecting the test type of score (Miettinen & Nurminen) in the confidence intervals for two proportions [differences] module.

Table 14 Precision (Minimum Observed Difference and Two-sided 95% CI) Under Various Assumptions (With 268 participants (134 per arm) enrolled into the study)

Observed Clinical Response Rate of Treatment 2 at TOC visit	Minimum Observed Difference(%) required to achieve NI Margin of 12.5%	Estimated Treatment Difference (%) (Treatment 1 - Treatment 2)					
		0	-1	-2	-3	-4	-5
		Two-sided 95% CI of Estimated Treatment Difference (%)					
82%	-1.50	(-10.84, 10.84)	(-11.94, 9.94)	(-13.04, 9.03)	(-14.13, 8.13)	(-15.22, 7.22)	(-16.30, 6.31)
86%	-2.27	(-9.92, 9.92)	(-11.06, 9.03)	(-12.19, 8.14)	(-13.31, 7.24)	(-14.42, 6.35)	(-15.53, 5.45)
90%	-3.17	(-8.78, 8.78)	(-9.96, 7.90)	(-11.14, 7.02)	(-12.30, 6.14)	(-13.45, 5.26)	(-14.60, 4.38)
94%	-4.19	(-7.31, 7.31)	(-8.58, 6.44)	(-9.83, 5.58)	(-11.05, 4.71)	(-12.26, 3.85)	(-13.46, 2.98)

Note: The 95% CI is calculated based on 100 participants per each treatment group expected to be included in the analysis in the CE population.

9.10 Subgroup Analyses and Effect of Baseline Factors

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- APACHE II Score (≤10 vs. >10)
- Baseline renal CrCL (30 to ≤50 vs. >50 mL/min)

- Procedure Type (percutaneous aspiration, laparoscopy, laparotomy, other)
- Prior antibiotic use (yes or no)
- Sex (female, male)
- Primary Site of Infection Stratum: bowel [small or large] vs. other site of cIAI
- Anatomic site of infection/diagnosis
- Pathogens
- Presence of baseline bacteremia
- Number of baseline pathogens (polymicrobial, monomicrobial).
- Number of Abscesses (single, multiple)
- Peritonitis Type (local, diffuse)
- Site of infection (appendix, non-appendix)
- Pathogen MIC and Pathogen Classification

9.11 Compliance (Medication Adherence)

Considering this is an IV study conducted by investigators/nurses, it is expected to follow the protocol strictly without compliance issues. Any non-compliance dosage will be monitored and recorded.

9.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics by treatment group.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

There are no governance committees in this study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

Laboratory tests for hematology, coagulation, chemistry and urinalysis are specified in Table 15.

Table 15 Laboratory Tests

Hematology	Coagulation	Chemistry	Urinalysis	Other
Hematocrit	Partial Prothrombin time	Albumin	Blood	Follicle Stimulating Hormone (FSH)
Hemoglobin	Prothrombin time	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG)
Platelet count		Alanine aminotransferase (ALT)	Protein	
WBC (total and differential)		Aspartate aminotransferase (AST)	Specific gravity	
		Lactic dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	
		Calcium		
		Chloride		
		Creatinine		
		Glucose		
		Phosphorus		
		Potassium		
		Sodium		
		Total Bilirubin		
		Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
		Total protein		
		Blood Urea Nitrogen or Blood Urea		

All blood and urine samples for safety laboratory testing (hematology, coagulation, chemistry and urinalysis) will be sent to local safety laboratory for testing. Chemistry safety laboratory tests will be performed after at least an 8-hour fast. Non-fasting sample is acceptable for chemistry laboratory safety tests at screening.The timing for the collection of blood and urine samples for safety monitoring is provided in Section 1.3-SoA.

Approximate Blood Volumes Drawn by Study Visit and Sample Types

Study Visit	Screening	IV Study Treatment					Post-Treatment
	V1 Screening	V2 Randomization	V3	V 4	V 5	V 6 EOT	V7 TOC
Blood Parameter	Approximate Blood Volume (mL)						
Hematology	**2.0**			**2.0**		**2.0**	**2.0**
Blood for Coagulation	**4.0**			**4.0**		**4.0**	**4.0**
Serum/Plasma Chemistry	**3.5**			**3.5**		**3.5**	**3.5**
Serum β-HumanChorionic Gonadotropin (β-hCG)	**3.5**						**3.5**
Blood For LocalLaboratory Assessment of Creatinine[a]	**2.0**	**2.0**	**2.0**	**2.0**	**2.0**	**2.0**	**2.0**
Blood Specimen for Culture& Susceptibility	**40**	**As clinically Indicated (40mL/assessment)**					
Expected Total (mL)[bc]	55.0	2.0 or 42.0 if culture & susceptibility testing clinically indicated	2.0 or 42.0 if culture & susceptibility testing clinically indicated	11.5 or 51.5 if culture & susceptibility testing clinically indicated	2.0 or 42.0 if culture & susceptibility testing clinically indicated	11.5 or 51.5 if culture & susceptibility testing clinically indicated	15.0 or 55.0 if culture & susceptibility testing clinically indicated

a. On V1,V4,V6 and V7, perform if creatinine assessment not already done as part of 'blood for chemistry' assessment.
b. Additional blood samples may be collected in support of evaluation for an underlying etiology throughout the study. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder. Depending on the results of initial testing, additional blood volumes would be needed for further test such as HIV and/or viral hepatitis testing.
c. Culture for blood sample at screening is conducted as clinically indicated in participants with :1) hospital-acquired infections;2) for those who have failed prior antibacterial therapy; or 3) who have signs of severe sepsis as assessed by the investigator.
In addition, if signs of sepsis appear or the subject is assessed as a treatment failure at any time on study (including EOT, TOC visit), a blood culture should be taken.
At each blood culture collection, approximately 40 mL, two sets (from two separate blood draws) of blood cultures (each set consisting of an aerobic and an anaerobic bottle) are collected: 2 sets of blood cultures (10 mL x 2 = 20mL)/aerobic culture; (10 mL x 2 = 20 mL)/anaerobic culture.
Blood culture is conducted at appropriate frequency until negative. Blood cultures will be performed at the local microbiology laboratory according to recognized methods and per each laboratory's standard precedures and isolates sent to the central microbiology laboratory.

Local Laboratory Monitoring for Renal Function

Specifically, for the purpose of monitoring an individual participant's renal function in "real time", a creatinine assessment should be performed at the local laboratory on the visit specified in SoA.

For participants with renal insufficiency or whose creatinine clearance changes during treatment with study therapy (refer to Table 3 and Table 4 in Section 6.6), the dose of study drug must be adjusted based upon the degree of renal function impairment as determined by the estimated or actual creatinine clearance.

Results of these local laboratory tests must be documented in the appropriate eCRF. Laboratory abnormalities resulting in an adverse event or dose adjustment should also be collected on the appropriate eCRF. Any clinically relevant laboratory test abnormality that emerged during study therapy and was considered by the investigator to be an adverse event or event of clinical interest should be repeated until the abnormal value has normalized, stabilized, or returned to baseline.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant

number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill

count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

- (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study); or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

  - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

  - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
    - The following are not acceptable methods of contraception:
        - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).
        - Male and female condom cannot be used together.
    - A combination of male condom with either cap, diaphragm or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 16 consistently and correctly during the protocol-defined time frame in Section 5.1.

Table 16 Contraceptive Methods

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,d] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,d] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] Male condoms must be used in addition to hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative pregnancy test has been confirmed at screening. Prior documentation of a negative serum β-HCG within 2 days (48 hours) of enrollment is acceptable for women of reproductive potential. If documentation is not available, a serum pregnancy test will be required..

Additional serum pregnancy testing will be performed at the Day 28 post-randomization visit.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: APACHE II Severity of Disease Classification System – APACHE II Score Form

A. Acute Physiology Score:

		HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	PHYSIOLOGIC VARIABLE	+4	+3	+2	+1	0	+1	+2	+3	+4
1	Temperature rectal (°C)	□ ≥41	□ 39-40.9		□ 38.5-38.9	□ 36.0-38.4	□ 34-35.9	□ 32-33.9	□ 30-31.9	□ ≤29.9
2	Mean arterial pressure (mmHg) = (2 x diastolic + systolic)/3	□ ≥160	□ 130-159	□ 110-129		□ 70-109		□ 50-69		□ ≤49
3	Heart rate (ventricular response)[a]	□ ≥180	□ 140-179	□ 110-139		□ 70-109		□ 55-69	□ 40-54	□ ≤39
4	Respiratory rate (nonventilated or ventilated)	□ ≥50	□ 35-49		□ 25-34	□ 12-24	□ 10-11	□ 6-9		□ ⩽5
5	Oxygenation A-aDO_2 or PaO_2 (mm Hg) a)FiO_2≥0.5:record A-aDO_2	□ ≥500	□ 350-499	□ 200-349		□ <200				
	b)FiO_2<0.5:record only PaO_2					□ >70	□ 61-70		□ 55-60	□ <55
6	Arterial pH (*If no ABGs record Serum HCO_3 below)	□ ≥7.7	□ 7.6-7.69		□ 7.5-7.59	□ 7.33-7.49		□ 7.25-7.32	□ 7.15-7.24	□ <7.15
7	Serum Sodium (mMol/L)	□ ≥180	□ 160-179	□ 155-159	□ 150-154	□ 130-149		□ 120-129	□ 111-119	□ ≤110
8	Serum Potassium (mMol/L)	□ ≥7	□ 6-6.9		□ 5.5-5.9	□ 3.5-5.4	□ 3-3.4	□ 2.5-2.9		□ <2.5
9	Serum Creatinine (mg/dL) Double Point for acute renal failure	□ ≥3.5	□ 2-3.4	□ 1.5-1.9		□ 0.6-1.4		□ <0.6		
10	Hematocrit (%)	□ ≥60		□ 50-59.9	□ 46-49.9	□ 30-45.9		□ 20-29.9		□ <20

		HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	PHYSIOLOGIC VARIABLE	+4	+3	+2	+1	0	+1	+2	+3	+4
11	White Blood Count (total/mm^3) (in 1000's)	□ ≥40		□ 20-39.9	□ 15-19.9	□ 3-14.9		□ 1-2.9		□ <1
12	Glasgow Coma Scale Enter 15 minus actual GCS –see calculations in table below	15-GCS =								
A	Total Acute Physiology Score (APS)	Sum of the 12 individual variable points =								
*	Serum HCO_3(venous-mMol/L) (Not preferred, use if no ABGs)	□ ≥52	□ 41-51.9		□ 32-40.9	□ 22-31.9		□ 18-21.9	□ 15-17.9	□ <15

APACHE II Severity of Disease Classification System

Glasgow Coma Score (GCS) (circle appropriate response)		
Eyes open (E) 4 - spontaneously 3 - to verbal command 2 - to painful stimul 1 - no response	Motor response (M) 6 - to verbal command 5 - localizes to pain 4 - withdraws to pain 3 - decorticate 2 - decerebrate 1 - no response	Verbal - Response (V) 5-oriented and controversed 4-confused and disoriented 3-inappropriate words 2-incomprehensible sounds 1-no response
GLASGOW COMA SCORE† = E + M + V		
†Participants scoring 3 or 4 have an 85% chance of dying or remaining vegetative, while scores above 11 indicate 5 to 10% likelihood of death or vegetative state and 85% chance of moderate disability or good recovery. Intermediate scores correlate with proportional chances of participants recovering.		
B. Age Points		
Age Points ≤44 0 45-54 2 55-64 3 65-74 5 ≥75 6 Age points = _____		

C. Chronic Health Points (CHE)
If any of the 5 CHE categories is answered with yes give +5 points for nonoperative or emergency postoperative participants, or +2 points for elective postoperative participants Liver - Cirrhosis with Portal Hypertension (PHT) or encephalopathy Cardiovascular - NYHA Class IV angina or at rest or with minimal self-care activities Pulmonary - chronic hypoxemia or hypercapnia or polycythemia or pulmonary hypertension of PHT >40 mm Hg Kidney - chronic peritoneal or hemodialysis Immune - immune compromised host Chronic Health Points=_____
APACHE-II Score is sum of A+B+C APS points A _____ Age points +B _____ Chronic Health Points +C _____ Total APACHE-II Score=_____

[a] Heart rate is recommended when determining the APACHE II score during screening. But if pulse rate is collected, it could be accepted.

Adapted from: [Knaus, W. A., et al 1985]

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ABG	Arterial Blood Gas
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase (SGPT)
APACHE	Acute Physiology and Chronic Health Evaluation
APaT	All Participants as Treated
AST	Aspartate Aminotransferase (SGOT)
AUC	Area Under the Concentration-time Curve
β-hCG	β-Human Chorionic Gonadotropin
BLI	β-lactamase Inhibitor
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CI	Confidence Interval
cIAI	Complicated Intraabdominal Infection
C_{max}	Maximum Concentration
CNDA	China National Drug Administration
CrCL	Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DILI	Drug-induced Liver Injury
ECG	Electrocardiogram
ECI	Event of Clinical Interest
eCRF	Electronic Case Report Form
EDC	Electronic Data Collection
EMA	European Medicines Agency
EOT	End-of-Therapy
ESBL	Extended-spectrum -lactamase
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FiO_2	Fraction of inspired oxygen
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Glasgow coma score
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
IAI	Intraabdominal infection
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous(ly)
IVRS/IWRS	Interactive Voice Randomization System/Web Randomization System
LAM	Lactational Amenorrhea Method
LDH	Lactate Dehydrogenase
LFU	Late Follow-up

Abbreviation	Expanded Term
ME	Microbiologically Evaluable
MIC	Minimum Inhibitory Concentration
MITT	Microbiological Intent-to Treat
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSD	Merck & Co, Inc. (Merck Sharp & Dohme outside the US)
PaO_2	Partial Pressure of Oxygen
PBP	Penicillin-binding proteins
Q8h	Every 8 hours
Q12h	Every 12 hours
PD	Pharmacodynamic
PDLC	Pre-Defined Limit of Change
PI	Principal Investigator
PK	Pharmacokinetic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STAR	Staged Abdominal Repair
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOC	Test-of-Cure
WOCBP	Woman/Women of Childbearing Potential

11 REFERENCES

[Knaus, W. A., et al 1985]	Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Apache II: A severity of disease classification system. Crit Care Med 1985;13(10):818-29.	[03RRCS]
[Lee, Y. R., et al 2015]	Lee YR, McMahan D, McCall C, Perry GK. Complicated intra-abdominal infections: the old antimicrobials and the new players. Drugs. 2015;75:2097-117.	[05020W]
[Qiao-juan, H., et al 2010]	Qiao-juan H, Zhi-dong H, Jin L, Bin T, Hai-ru X, Jing L. 2008 Mohnarin report: bacterial distribution and resistance in intra-abdominal infections [abstract]. Chinese Journal of Antibiotics. 2010;35(8):620-25.	[05025F]
[Sartelli, M., et al 2014]	Sartelli M, Catena F, Ansaloni L, Coccolini F, Corbella D, Moore EE, et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study. World J Emerg Surg. 2014 May 14;9:37.	[04483T]
[Solomkin, J. S., et al 2010]	Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJC, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the surgical infection society and the infectious diseases society of America. Clin Infect Dis 2010;50:133-64.	[03RBW3]
[Solomkin, J., et al 2015]	Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J,et al. Ceftolozane/Tazobactam plus Metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: Results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis. 2015 May 15;60(10):1462-71.	[04NRTL]
[U.S. Prescribing Information 2016]	U.S. Prescribing Information: ZERBAXA (ceftolozane and tazobactam) for injection, for intravenous use: 2016.	[04PH7J]

[Yang, Q., et al 2010]	Yang Q, Wang H, Chen M, Ni Y, Yu Y, Hu B, et al. Surveillance of antimicrobial susceptibility of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in China: the 2002-2009 Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents 2010;36:507-12.	[03RBVL]
[Zhang, H., et al 2014]	Zhang H, Yang Q, Xiao M, Chen M, Badal RE, Xu Y. Antimicrobial susceptibility of Gram-negative bacteria causing intra-abdominal infections in China: SMART China 2011. Chin Med J (Engl). 2014;127(13):2429-33.	[05023K]

Supplemental Statistical Analysis Plan (sSAP)

MK-7625A-015

A Phase 3, Multicenter, Double-blind, Randomized, Active-controlled Clinical Study to Evaluate the Efficacy and Safety of Ceftolozane/Tazobactam (MK-7625A) plus Metronidazole Versus Meropenem in Chinese Participants with Complicated Intra-abdominal Infection

TABLE OF CONTENTS

LIST OF TABLES

1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

Changes for Amendment 1:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
3.5.1	Efficacy Analysis Populations	CE population inclusion criteria #3 was changed from 4 days to 3 days;	Changes are made to be consistent with global pivotal studies. Details of exclusion criteria provided in the Appendix.
3.6.1	Statistical Methods for Efficacy Analyses	Add information for exploratory endpoints	Provide details in analysis method for exploratory endpoints
3.10	Subgroup Analyses and Effect of Baseline Factors	Remove "Region" in the subgroup analyses and add statistical method for subgroup analyses.	Changes are made to be consistent with updated protocol (v01)
3.11	Compliance (Medication Adherence)	Add formula and details for calculation of compliance	Provide more details on compliance calculation
3.12	Extent of Exposure	Add analysis method	Provide details on the tabulation of extent of exposure

Changes for Amendment 2:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
3.1	Statistical Analysis Plan Summary	Clarify data source of the stratification factor used for efficacy and sensitivity analyses where the stratified method is applied if ≥10% of participants are mis-stratified.	The eCRF stratum will be primary for efficacy analyses; randomization stratum from IVRS/IWRS will be supportive for the sensitivity analysis.
3.4.1	Efficacy Endpoints	Add exploratory analysis for superinfection and new infection	Changes are made to be consistent with protocol 8.2.2.
3.5.1	Efficacy Analysis Populations	Clarify the MITT population	Changes are made to clarify the inclusion criteria for the MITT population and to be consistent with the definition in the evaluability guideline.
3.6.1	Statistical Methods for Efficacy Analyses	Change the stratified M&N method to the unstratified M&N method for secondary efficacy analyses related to per-pathogen groups	Due to reduced sample sizes at per-pathogen groups.
		Add analysis for superinfection and new infection	Changes are made to be consistent with protocol 8.2.2.
3.6.2	Statistical Methods for Safety Analyses	PDLC analyses were removed from Tier 2 and Tier 3 analyses.	The PDLC analyses are not applicable for this study compound; change from baseline

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
			will also be evaluated based on DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) criteria.
3.10	Subgroup Analyses and Effect of Baseline Factors	Update APACHE II categorization and provide details for pathogen MIC and pathogen classification;	Changes are made to be consistent with pivotal studies and efficacy analysis populations across this study compound program.
		Clarify subgroup analyses for the CE population and add subgroup analyses for the MITT/ITT population.	
3.12	Extent of Exposure	Adjust calculation of exposure (in days); add exposure summary for the CE population	Provide clarification on the tabulation of extent of exposure.

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.1 through 3.12.

Study Design Overview	A randomized, active-controlled, parallel-group, multicenter, double-blind study of ceftolozane/tazobactam IV infusion (1500 mg q8h) plus metronidazole (500 mg q8h) IV infusion vs. meropenem IV (1000 mg q8h) plus placebo in Chinese participants with cIAI.
Treatment Assignment	*Randomization method*: Participants will be randomized in a 1: 1 ratio to two treatment arms of the study, Treatment 1 (ceftolozane/tazobactam + metronidazole) group or Treatment 2 (meropenem + placebo) group. Both treatments will be administered IV q8h. *Stratification method*: Randomization will be stratified by anatomic site of infection (bowel [small or large] vs. other site of cIAI). Participants with appendix, stomach, or duodenum as the anatomic site of infection, will be stratified to the "other site" group during the randomization process.

	All efficacy analyses where the stratified method is applied will be performed based on eCRF stratum (actual stratum); the sensitivity analysis for the primary efficacy endpoint will be performed using the randomized stratum from the interactive voice/web response system (IVRS/IWRS), if any mis-stratification occurs. *Double-dummy double-blind method*: A double-blinding technique will be used. Study drug will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or unblinded qualified study site personnel. The participant, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment administration or clinical evaluation of the participants are unaware of the group assignments
Analysis Populations	Primary Efficacy Analysis: Clinical evaluable (CE) population. Secondary Efficacy Analysis: Intent-to-treat (ITT) population, microbiological intent-to-treat (MITT) population, microbiologically evaluable (ME) population and expanded microbiologically evaluable (EME) population. Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	Clinical response at the TOC visit
Secondary Endpoints	Clinical response at the EOT visit Microbiological response (Per-subject and per-pathogen microbiological response) at the TOC visit
Statistical Methods for Key Efficacy	For the primary hypothesis (clinical response rate at the TOC visit in the CE population), Treatment 1 (ceftolozane/tazobactam + metronidazole) will be considered non-inferior to Treatment 2 (meropenem + placebo) if the lower bound of the 2-sided 95% confidence interval (CI) for the between-treatment difference in the clinical response rate (Treatment 1 minus Treatment 2) is larger than -12.5%. The two-sided 95% CIs for between-treatment differences in the clinical response rate will be calculated using the stratified Miettinen and Nurminen method with the Cochran-Mantel-Haenszel (CMH) weighting. For secondary objectives, point estimates and two-sided 95% CIs will be calculated using the same stratified Miettinen and Nurminen method as described above.
Statistical Methods for Key Safety Analyses	P-values (Tier 1 only) and 95% CIs (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the unstratified Miettinen and Nurminen method.
Interim Analyses	A blinded review of the clinical response rate will be ongoing during the study. The impact of the blinded clinical response rate on the assumptions underlying the power/sample size calculation will be formally assessed by the Sponsor when approximately 75% of the planned sample size (N=201) have completed TOC visits or sooner if enrollment or event rates are occurring faster than anticipated. If the clinical response rate at the TOC visit is lower than the 90% assumed in the power calculation, consideration will be given to increasing the sample size. There are no plans to conduct a formal interim analysis of unblinded efficacy data in the study.
Multiplicity	No multiplicity adjustment is planned as there is a single comparison of 2 treatments using 1 endpoint in the primary hypothesis. Other efficacy analyses will be considered supportive and/or explanatory.
Sample Size and Power	The planned sample size is 268 participants (134 per arm). Assuming a 75% evaluability rate in the CE population, it is expected that 200 CE

	participants (100 participants per arm) will be included. For the clinical response rate at the TOC visit in the CE population, the study has 80% power to demonstrate that Treatment 1 (ceftolozane/tazobactam + metronidazole) is non-inferior to Treatment 2 (meropenem + placebo) using a 1-tailed alpha of 2.5%, if there is no underlying treatment difference. The power and sample size are based on the following assumptions: 1) a non-inferiority margin of -12.5%, and 2) an underlying clinical response rate of 90% in the CE population for both treatments.

3.2 Responsibility for Analyses/In-House Blinding

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study. Unblinded Sponsor personnel [ie. unblinded CRA (uCRA), unblinded data manager (uDM), unblinded clinical scientist (uCS)], will be assigned to support the oversight and monitoring of study conduct. The uCRA will ensure that unblinded monitoring activities are conducted in compliance with protocol and regulatory requirements and the Trial Specific Site Monitoring Plan. The uDM will perform data review and reconciliation for unblinded eCRF data. The uCS will provide support and guidance on study-specific unblinded procedure-related questions, in particular, questions related to the blinded clinical supplies as well as support for the uDM on data review issues requiring consultation.

The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice/web response system (IVRS/IWRS).

3.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3 of the protocol.

Non-Inferiority Margin Justification:

A conservative method for estimating the treatment difference is adopted by comparison of the lower bound of the 95% CI for the antibacterial drug therapy and the upper bound of the 95% CI for placebo/no treatment. The source data were obtained from the previous pivotal studies or medical literature. An upper bound of the 95% CI of 64.9% for placebo/no treatment was directly obtained from 2015 FDA Guidance for Industry *Complicated Intra-Abdominal Infections: Developing Drugs for Treatment*. For antibacterial drug therapy, a meta-analysis for the clinical response rates was applied using study results from the two most commonly used cIAI drugs; meropenem and imipenem/cilastatin [Table 1]. In this meta-analysis, a point estimate of 87.8% with a two-sided 95% CI of 84.9% and 90.8% was calculated. For consistency of analyses, the DerSimonian and Laird method using random

effects was applied to both the above mentioned FDA guidance and the antibacterial drug results in [Table 1].

Given an estimated treatment difference of 20.0% (84.9% minus 64.9%) and consideration of a 12.5% NI margin suggested by EMA guidance *Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 REV 2) to address indication-specific clinical data*, the non-inferiority margin is selected to be 12.5%, which represents preserving about 40% of the estimated treatment difference of 20%, as shown above.

Table 1 Clinical response rate at TOC visit

Drug	Clinical response rate at TOC n/N(%[95%CI])	Source	Note
Meropenem	364/417 87.3% [83.75, 90.15]	CXA-cIAI-10-08-09	Global study
Imipenem/cilastatin	50/55 90.9% [80.0, 97.0]	Chen et al. BMC Infectious Diseases 2010, 10:217	Chinese participants

3.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

3.4.1 Efficacy Endpoints

A full description of the efficacy measures is provided in Section 4.2.1.1 of the protocol.

The primary efficacy endpoint is the clinical response rate at the TOC visit in the CE population.

The secondary efficacy endpoints are:

(1) Clinical response at the TOC visit in the ITT population.
(2) Clinical response at the EOT visit in the ITT and CE population.
(3) Percentage of participants achieving a favorable microbiological response at the TOC visit in the EME population.

(4) Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the TOC visit in the EME population.

The exploratory efficacy endpoints are:

(1) Clinical response at the TOC visit in the MITT and ME populations.
(2) Clinical response at the EOT visit in the MITT population.

(3) Percentage of participants achieving a favorable microbiological response at the TOC visit in the ME and MITT populations.

(4) Percentage of participants achieving a favorable microbiological response at the EOT visit in the ME, EME and MITT populations.

(5) Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the TOC visit in the ME and MITT populations.

(6) Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the EOT visit in the ME, EME and MITT populations.

(7) Percentage of participants with superinfection or new infection (defined in the protocol Table 7) in the MITT population.

3.4.2 Safety Endpoints

The descriptions of safety measurements are provided in Section 4.2.1.2 of the protocol.

Based upon a review of adult and pediatric trial safety data, no Tier 1 AEs of clinical interest have been identified. The broad clinical and laboratory adverse event (AE) categories, consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug related and serious, discontinuation of IV study therapy due to an AE, discontinuation of IV study therapy due to a drug-related AE, and an AE leading to death will be considered Tier 2 endpoints.

3.5 Analysis Populations

3.5.1 Efficacy Analysis Populations

The Clinically Evaluable (CE) population will serve as the primary population for the analysis of efficacy data in this study. The Intent-to-Treat (ITT), Microbiological Intent-to-treat (MITT), Microbiologically Evaluable (ME) and Expanded Microbiologically Evaluable (EME) populations will serve as secondary or exploratory populations for efficacy analyses.

The ITT population will consist of all randomized participants. Participants in the ITT population will be analyzed based on the treatment they were randomized to, irrespective of what they actually received.

The MITT population will consist of all randomized participants who have a baseline intra-abdominal bacterial pathogen known to cause cIAI, regardless of susceptibility to study drug. Participants in the MITT population will be analyzed based on the treatment they were randomized to, irrespective of what they actually received.

The CE population is a subset of the ITT population who also meet the following key criteria:

1. Meet the protocol definition of cIAI,
2. Have no significant deviation from the protocol that could impact the assessment of efficacy,
3. Receive the minimum duration of IV study therapy (3 days, unless a treatment failure prior to day 3) that participant was randomized to and
4. Have an efficacy assessment of cure or failure at the TOC visit.

The CE population does not require a bacterial pathogen identified as the cause of cIAI.

Details of exclusion criteria will be provided in Appendix I.

The ME population is the subset of CE participants who have at least one baseline intraabdominal pathogen identified that is susceptible to study drug.

The EME population consists of all randomized participants who have cIAI as evidenced by identification of at least 1 baseline intra-abdominal pathogen, regardless of susceptibility to study drug and meet all CE population criteria.

The CE, ME, and EME populations will serve as the per-protocol analysis populations for the analysis of efficacy data in this study.

3.5.2 Safety Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

For the analysis of pre-specified events of interest described above in Section 3.4.2, participants will be excluded from specific analyses if the conditions defining the event were present at randomization (Day 1).

3.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 3.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 3.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size limitations, etc. Unless otherwise stated, all statistical tests will be conducted at α=0.025 (1-sided) level.

3.6.1 Statistical Methods for Efficacy Analyses

Primary Efficacy Analysis

The primary objective is to establish non-inferiority of Treatment 1 (ceftolozane/tazobactam + metronidazole) to Treatment 2 (meropenem + placebo) with respect to clinical response rate in the CE population at TOC visit. 95% CIs for between-treatment differences in the clinical response rate will be calculated using the stratified Miettinen and Nurminen (M&N) method (1985) with the Cochran-Mantel-Haenszel (CMH) weighting. The analyses will be stratified by anatomic site of infection (bowel [small or large] vs. other site of cIAI). Treatment 1 (ceftolozane/tazobactam + metronidazole) will be considered non-inferior to Treatment 2 (meropenem + placebo) if the lower bound of the 2-sided 95% CI of the between-treatment difference in clinical response rate (Treatment 1 minus Treatment 2) at TOC in the CE population is larger than -12.5%.

Secondary Efficacy Analysis

The secondary efficacy analyses will follow the same stratified M&N method described above for the primary efficacy analysis except the per-pathogen microbiological responses will be analyzed using the unstratified M&N method. The estimates and their two-sided 95% CIs will be calculated for each secondary efficacy endpoint. The secondary efficacy objectives are estimation objectives only, so no NI testing will be applied on the secondary efficacy analyses.

Exploratory Efficacy Analysis

The exploratory efficacy analyses will follow the M&N method, unless otherwise specified. Details of statistical method are provided in [Table 2]. The estimates and their two-sided 95% CIs will be calculated for each exploratory efficacy endpoint. The exploratory efficacy objectives are estimation objectives only, and no hypothesis testing will be applied.

The percentage of participants with superinfection or new infection for the MITT population will only be summarized.

Missing Values

Any participant missing an evaluation for a specific endpoint (clinical or microbiological) at any particular visit will be generally considered as being “indeterminate” for that endpoint in the ITT and MITT populations. Participants with an indeterminate clinical outcome will be

considered as "Treatment Failure" in the ITT and MITT analysis populations. Participants with an indeterminate clinical outcome will be excluded from per-protocol analysis populations (CE, ME and EME). The following are exceptions to this rule:

- Participants discontinuing IV study therapy due to lack of efficacy (i.e., withdrawals with subsequent non-study antibiotic therapy or participants requiring therapy beyond 14 days) will be considered as "failures" with respect to clinical response at the time of discontinuation and all subsequent time points in all populations.

- Participants discontinuing IV study therapy due to lack of efficacy will be presumed to have persistence for the microbiological response at the time of discontinuation and all subsequent time points.

The primary and secondary endpoints, primary and secondary analysis populations, and statistical methods that will be employed for the efficacy analyses are presented in [Table 2]. Since a favorable clinical response and a favorable microbiological response require a clear assessment, an assessment of "indeterminate" would be considered treatment failure in the ITT and MITT populations.

Table 2 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis:			
Clinical response at the TOC visit	Stratified M&N‡	CE§	DAO††
Secondary Endpoints:			
Clinical response at the TOC visit	Stratified M&N‡	ITT%	M=F‡‡
Clinical response at the EOT visit	Stratified M&N‡	ITT% CE§	M=F‡‡ DAO††
Percentage of participants achieving a favorable microbiological response at the TOC visit	Stratified M&N‡	EME#	DAO††
Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the TOC visit	Unstratified M&N‡	EME#	DAO††
Exploratory Endpoints:			
Clinical response at the TOC visit	Stratified M&N	MITT¶ ME#	M=F‡‡ DAO††
Clinical response at the EOT visit	Stratified M&N	MITT¶	M=F‡‡

Endpoint/Variable (Description, Time point)	Statistical Method†	Analysis Population	Missing Data Approach
Percentage of participants achieving a favorable microbiological response at the TOC visit	Stratified M&N	ME#	DAO††
		MITT¶	M=F‡‡
Percentage of participants achieving a favorable microbiological response at the EOT visit	Stratified M&N	ME#	DAO††
		EME#	DAO††
		MITT¶	M=F‡‡
Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the TOC visit	Unstratified M&N	ME#	DAO††
		MITT¶	M=F‡‡
Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the EOT visit	Unstratified M&N	ME#	DAO††
Per-pathogen percentage of baseline intra-abdominal pathogens achieving a favorable microbiological response at the EOT visit	Unstratified M&N	EME#	DAO††
		MITT¶	M=F‡‡

† Statistical models are described in further detail below:

‡ M&N is Miettinen and Nurminen method stratified by anatomic site of infection (bowel [small or large] vs. other site of cIAI).

§ CE population is a subset of the ITT population who also meet the following criteria:1) Meet the protocol definition of cIAI; 2) Have no significant deviation from the protocol that could impact the assessment of efficacy,3) Receive the minimum duration of IV study therapy (3 days unless treatment failure prior to Day 3), and 4) Have a efficacy assessment of Cure or Failure at the time point of interest.

% ITT population consists of all randomized participants.

¶ MITT population: consist of all randomized participants who have a baseline intra-abdominal bacterial pathogen known to cause cIAI.

ME population is the subset of CE participants who have at least one baseline intraabdominal pathogen identified that is susceptible to study drug. EME population is expanded ME population.

†† DAO is data as observed, that is, participants with missing values will be excluded from the analysis.

‡‡ M=F is missing =failure

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and multiple time points is described in Section 3.7, Interim Analyses and in Section 3.8, Multiplicity.

3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs.

The analysis of safety results will follow a tiered approach [Table 3]. The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory and vital signs are either pre-specified as "Tier-1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or adverse events of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol based upon a review of adult and pediatric trial safety data.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (also via the M&N method (1985)). Membership in Tier 2 requires that at least 4 participants in at least one treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change. In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 endpoints.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

Continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 3 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	None	X	X	X
Tier 2	Any AE‡		X	X
	Any Serious AE		X	X
	Any AE leading to death		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs or SOCs† (incidence ≥4 of participants in one of the treatment groups)		X	X
Tier 3	Specific AEs or SOCs† (incidence <4 of participants in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X

† Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints.

‡ Indicates broad AE category of the number of participants reporting any adverse event.

Note: SOC=System Organ Class; X = results will be provided.

3.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment using descriptive statistics for continuous or categorical variables, as appropriate.

3.7 Interim Analyses

An internal blinded sample size re-estimation will be conducted as described in the next paragraph. There are no plans to conduct a formal interim analysis of unblinded efficacy data in the study.

Blinded review of clinical response rate at TOC visits on the CE population will be ongoing during the study. The impact of the clinical response rate on the assumptions underlying the power/sample size calculation will be formally assessed when approximately 75% (N=201) of the planned sample size (N=268) have completed TOC visits or sooner if enrollment or event rates are occurring faster than anticipated. In consideration of having enough time for blinded sample size re-estimation as well as a stable estimate for the clinical response rate, 75% is selected as the time point for the blinded sample size assessment.

If the observed, blinded (pooled) clinical response rate is lower than the 90% assumed in the power calculation, consideration will be given to increasing the overall sample size as outlined in [Table 4]. If the observed clinical response rate is larger than 90%, the overall sample size will be maintained at the planned N=268 as the power for this endpoint/hypothesis will likely exceed 80%. The maximum sample size will not exceed N=408 (204 per group) regardless of the observed clinical response rate.

Blinded review of clinical response is not a true interim analysis in that it will not require a dataset freeze, unblinding, and multiplicity adjustments. The accruing database will not be officially locked for this blinded sample size re-estimation; however, all data relating to the assessment of clinical response rate will be cleaned and all queries resolved before the formal assessment of the clinical response rate. As this sample size re-estimation will be done in a blinded fashion, there is no impact on type 1 error rates.

Table 4 Sample Size Adjustments based on Interim Blinded Review of Clinical Response Rate at TOC Visit

Observed Clinical Response Rate†	Power based on Original Sample Size (N=268) (%)	Revised Sample Size‡	Percent Increase from Original Sample Size (%)
89%	77.2	294	9.7
88%	74.6	310	15.7
87%	72.2	328	22.4
86%	70.0	344	28.4
85%	67.9	360	34.3
84%	66.0	376	40.3
83%	64.0	392	47.3
82%	62.2	408	52.2

† This rate is expressed as a percent and rounded to the nearest integer value.

‡ Calculated to provide 80% power based on the observed clinical response rate and assumed evaluable rate of 75% in CE population in the power/sample size calculation.

Note: The calculation is also based on the assumptions from the sample size section, i.e. one-sided 2.5% alpha-level, no underlying treatment difference, and NI margin of -12.5%.

3.8 Multiplicity

As there is only a single primary efficacy hypothesis which is being conducted at the one -sided α=0.025 level, no multiplicity adjustment is needed for the primary efficacy analysis.

The secondary efficacy objectives are estimation objectives, are supportive in nature and have no associated hypotheses. Therefore, no multiplicity adjustment is necessary for the secondary efficacy analysis.

There will be no multiplicity adjustments applied to the safety summaries.

3.9 Sample Size and Power Calculations

3.9.1 Sample Size and Power for Efficacy Analyses

This study will randomize 268 participants (134 per treatment arm) into the study and has 80% power to establish that Treatment 1 (ceftolozane/tazobactam + metronidazole) is non-inferior to Treatment 2 (meropenem + placebo) in the clinical response rate at the TOC visit in CE population at an overall one-sided, 2.5% alpha-level, if there is no underlying treatment difference. The power and sample size are based on the following assumptions: 1) an approximately 75% evaluable rate in CE population 2) a non-inferiority margin of -12.5% (Treatment 1 minus Treatment 2), and 3) an underlying clinical response rate of 90% at the TOC visit. Above assumption is based on the pivotal study CXA-cIAI-10-08-09 CSR. The non-inferiority margin is regarded as the minimum difference of clinical interest between the 2 treatments [rationale is described in Section 3.3]. The calculation is based on an asymptotic method proposed by Miettinen and Nurminen (1985) with 100 participants per group expected to be included in the analysis in CE population and is carried out using PASS by selecting the test type of likelihood score (Miettinen & Nurminen) in the non-inferiority & superiority tests for two proportions [differences] module. The minimum criterion for success is that the lower bound of the 95% CI on the treatment difference (Treatment 1 minus Treatment 2) > -12.5%. [Table 5] summarizes power calculations for the primary comparison under various assumptions.

Table 5 Power (%) Under Various Assumptions (With 268 participants (134 per arm) into the study and NI margin of -12.5%)

Underlying clinical response rate of treatment 2 at TOC visit	Underlying Treatment Difference（%） (Treatment 1 - Treatment 2)					
	2	1	0	-1	-2	-3
82%	76.9	69.9	62.2	54.3	46.4	38.7
84%	80.6	73.7	66.0	57.8	49.5	41.4
86%	84.4	77.7	70.0	61.6	52.9	44.4
88%	88.5	82.2	74.6	66.0	56.9	47.8
90%	92.6	87.2	80.0	71.4	61.9	52.0
92%	96.4	92.4	86.1	77.9	68.1	57.5
94%	99.0	96.9	92.5	85.5	76.1	65.0
Note: The power is calculated based on 100 participants per each treatment group expected to be included in the analysis in the CE population.						

Another way to assess the precision of a non-inferiority study is to consider the minimum observed difference that would just meet the criterion for non-inferiority (in this case, a lower bound of the 2-sided 95% CI for the difference in clinical response rate in CE population [Treatment 1 minus Treatment 2] that is just larger than -12.5%). This minimum observed difference will decrease as the observed clinical response rate in the control group increases [Table 6]. An observed clinical response rate of 90% in the treatment 2 will just meet the criterion for non-inferiority given an observed difference (Treatment 1 – Treatment 2) is not less than -3.2%, that is the observed clinical response rate in the treatment 1 is not less than 86.8%. An observed clinical response rate of 86% in the treatment 2 will just meet the criterion for non-inferiority given an observed difference (Treatment 1 – Treatment 2) is not less than -2.3%, that is the observed clinical response rate in the treatment 1 is not less than 83.7%. Above calculation is carried out using PASS by selecting the test type of score (Miettinen & Nurminen) in the CIs for two proportions [differences] module.

Table 6 Precision (Minimum Observed Difference and Two-sided 95% CI) Under Various Assumptions (With 268 participants (134 per arm) enrolled into the study)

Observed Clinical Response Rate of Treatment 2 at TOC visit	Minimum Observed Difference (%) required to achieve NI Margin of 12.5%	Estimated Treatment Difference（%） (Treatment 1 - Treatment 2)					
		0	-1	-2	-3	-4	-5
		Two-sided 95% CI of Estimated Treatment Difference (%)					
82%	-1.50	(-10.84, 10.84)	(-11.94, 9.94)	(-13.04, 9.03)	(-14.13, 8.13)	(-15.22, 7.22)	(-16.30, 6.31)
86%	-2.27	(-9.92, 9.92)	(-11.06, 9.03)	(-12.19, 8.14)	(-13.31, 7.24)	(-14.42, 6.35)	(-15.53, 5.45)
90%	-3.17	(-8.78, 8.78)	(-9.96, 7.90)	(-11.14, 7.02)	(-12.30, 6.14)	(-13.45, 5.26)	(-14.60, 4.38)
94%	-4.19	(-7.31, 7.31)	(-8.58, 6.44)	(-9.83, 5.58)	(-11.05, 4.71)	(-12.26, 3.85)	(-13.46, 2.98)

Note: The 95% CI is calculated based on 100 participants per each treatment group expected to be included in the analysis in the CE population.

3.10 Subgroup Analyses and Effect of Baseline Factors

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI except for baseline pathogen susceptibility) for the primary endpoint in the CE population will be estimated using the unstratified M&N method within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- APACHE II Score (<10 vs. ≥10)
- Baseline renal CrCL (30 to ≤50 vs. >50 mL/min)
- Procedure Type (percutaneous aspiration, laparoscopy, laparotomy, other)
- Prior antibiotic use (yes or no)
- Sex (female, male)
- Primary Site of Infection Stratum: bowel [small or large] vs. other site of cIAI
- Anatomic site of infection/diagnosis
- Baseline pathogens

- Presence of baseline bacteremia
- Number of baseline pathogens (polymicrobial, monomicrobial).
- Number of Abscesses (single, multiple)
- Peritonitis Type (local, diffuse)
- Site of infection (appendix, non-appendix)
- Baseline pathogen susceptibility to study treatment
- Baseline pathogen classification (ESBL status for baseline Enterobacteriaceae)

The baseline pathogen susceptibility to study treatment is categorized using the baseline pathogen MIC values. The subgroup analyses by baseline pathogen and by baseline pathogen susceptibility to study treatment will also be performed for the MITT population, and the rest of the subgroup analyses will also be performed for the ITT population.

3.11 Compliance (Medication Adherence)

Considering this is an IV study conducted by investigators/nurses, it is expected to follow the protocol strictly without compliance issues. Any non-compliance dosage will be monitored and recorded.

For each participant, percent compliance will be calculated using the following formula:

Compliance (%) = 100 times (Actual Number of Doses on Therapy) / (Total Number of Expected Doses on Therapy).

The "Total Number of Expected Doses on Therapy" is the total scheduled number of doses from the start of treatment administration to the last scheduled treatment administration for that participant based on Section 6.4 and 6.6 of the protocol. The "Actual Number of Doses on Therapy" is the total number of actual doses received from the start of treatment administration to the last treatment administration for that participant.

Compliance (%) will be categorized as: $< 80\%$, $\geq 80\%$ to $\leq 120\%$, $> 120\%$.

Summaries of percent compliance and compliance (%) categories will be provided for the CE population.

3.12 Extent of Exposure

The treatment duration for patients will be calculated as follows:

The duration of study drug exposure is calculated as difference between the last study therapy date and time and the first study therapy date and time converted to days plus 1 day.

The durations in days will be categorized into the following groups for the purpose of summaries: 1-3 days, 4-7 days, 8-10 days, 11-14 days, and > 14 days.

The extent of exposure (in days) to study treatment will be evaluated by summary statistics (n, mean, median, standard deviation, minimum, and maximum). Summaries will be tabulated by treatment group for the APaT and CE populations.

4. SUPPORTING DOCUMENTATION AND REFERENCES

4.1 Appendix I

Exclusion Criteria of the CE Population

Population	Reason
CE	Does not meet ITT eligibility
CE	Clinical Diagnostic Definition Not Met
CE	No Clinical Efficacy Assessment or Only Indeterminate Clinical Assessments
CE	TOC Assessment Performed Out of 24-45 days in study visit
CE	Prior Antibacterial Violation
CE	Concomitant Antibacterial Violation
CE	Confounding Antibacterial Post-treatment
CE	Participant with Previous Failure of Prior Antibiotic Therapy and Negative Intra-abdominal Specimen
CE	Participant Who Has Baseline Abscess Cannot Be Managed by Surgical Intervention Including Drainage
CE	Protocol Specified Minimum Duration of 3 Days of Study Therapy Not Received, unless treatment failure ≥ 48hours
CE	Maximum Protocol-Specified Duration of 14 Days of Study Therapy Exceeded
CE	Participant who missed 2 or more consecutive doses, or 3 or more non-consecutive doses which resulted in receiving <80% of the expected study treatment course, or >120% of expected study treatment course
CE	Confounding Medical Condition or Procedure
CE	Met Significant Deviation Per ERT Decision, Not Mentioned Above

4.2 References

[1] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.