Official Protocol Title:	A Phase 2, Randomized, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Plus Metronidazole Versus Meropenem in Pediatric Subjects with Complicated Intra-Abdominal Infection
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TITLE:

A Phase 2, Randomized, Active Comparator-Controlled, Multicenter, Double-Blind Clinical Trial to Study the Safety and Efficacy of Ceftolozane/Tazobactam (MK-7625A) Plus Metronidazole Versus Meropenem in Pediatric Subjects with Complicated Intra-Abdominal Infection

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	14-SEP-2020	Due to enrollment challenges in the remaining age groups in both this trial in pediatric subjects with cIAI (MK-7625A-035) and also in the companion trial in pediatric subjects with cUTI (MK7625A-034), individual study age group minimum requirements for Groups 3-5 were removed in both studies, and the overall combined enrollment minimum targets for Groups 3 and 5 were also reduced to facilitate more timely availability of these important pediatric data to health care providers and patients. These changes do not impact the key goals or scientific validity of either study.
Amendment 2	26-APR-2019	Enrollment targets for Groups 3-5 were applied across the present trial in pediatric subjects with cIAI (MK-7625A-035) and the companion trial in pediatric subjects with cUTI (MK-7625A-034).
Amendment 1/ Ukraine specific amendment	30-APR-2018	Country-specific amendment to exclude enrollment of subjects <2 years old (Groups 4 and 5) in Ukraine.
Original Protocol	21-MAR-2017	Not applicable.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1 4.2.1.1 5.2.1 5.4	Trial Summary Trial Design Rationale for Sample Size Intravenous Trial Treatments Stratification	Removed minimum number of at least 4 subjects per study (MK-7625A-034 and MK-7625A-035) in Groups 3, 4, and 5. Reduced minimum enrollment targets for Groups 3 and 5 across both studies.	Due to enrollment challenges in the remaining age groups, individual study age group minimum requirements for Groups 3-5 were removed in both the MK-7625A-034 and MK-7625A-035 studies. Additionally, the overall combined enrollment minimum targets for Groups 3 and 5 were reduced to facilitate more timely availability of these important pediatric data to health care providers and patients. These changes do not impact the key goals or scientific validity of either study.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	Updated text for informed consent process	Updated to align with Merck standard protocol template
5.1.2	Subject Inclusion Criteria		
5.1.3	Subject Exclusion Criteria		
5.10	Beginning and End of the Trial		
6	Trial Flow Chart		
7.1.1.1	Informed Consent/Assent		
7.1.1.1.1	General Informed Consent/Assent		
7.1.1.3	Subject Identification Card		
7.1.5.1	Screening		
7.2	Assessing and Recording Adverse Events		
7.2.2	Reporting of Pregnancy and Lactation to the Sponsor		
7.2.3.1	Serious Adverse Events		
7.2.3.2	Events of Clinical Interest		
10.1.2	Confidentiality of Subject Records		

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.1 5.1.2	Trial Design Subject Inclusion Criteria	Reworded language regarding the enrollment target for the percentage of subjects with a diagnosis of complicated appendicitis.	To provide additional flexibility in the number of subjects enrolled with a diagnosis of complicated appendicitis.
4.2.3.2.2	Microbiological Outcome	Removed language that emergent infections are considered to have an unfavorable microbiological response.	As microbiological outcome is meant to capture the persistence or eradication specifically of the baseline pathogen, emergent infections will not contribute to the microbiological outcome. This change aligns with other studies in the ZERBAXA program, wherein emergent infections are distinct from the overall microbiological outcome endpoint and are described separately in the CSR.
	Table 5: "Emergent Infection Categories"	Added "and through the TOC visit" to the definition of new infection.	To clarify the window in which new infections will be recorded.
5.1.3	Subject Exclusion Criteria	For chronic administration of systemic corticosteroids that could qualify as an immunosuppressing condition at screening, added the non-weight-based definition for participants weighing >20 kg.	To align the pediatric-specific definition of immunosuppression due to corticosteroid use with other protocols in the ZERBAXA program.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.2.5 6.0	Timing of Dose Administration Trial Flow Chart	Added text clarifying maximum duration of antibiotics.	To clarify that the final day of study treatment may extend into Day 15 to accommodate different start and stop times of the IV study treatment and/or dosing schedules of the oral step-down therapy.
5.8.1	Discontinuation of Treatment	Added "required for IV study treatment only" to discontinuation criteria for development of moderate or severe impairment of renal function.	The lower limit of 50 mL/min/1.73 m^2 only applies to ceftolozane/tazobactam and not to the various optional oral step-down treatment options.
5.10	Beginning and End of the Trial	Text defining the end of the trial as the last subject's last visit or contact was changed to defining the end of the trial as when the last data is available in either study, MK-7625A-034 or MK-7625A-035, whichever occurs later.	Updated to reflect the fact that the safety data will be combined for analysis across the 2 studies, thus the final analysis cannot begin until both studies are completed and final data from both trials are available.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.4.4	Subject Blinding/Unblinding	Updated template text to describe who may be unblinded following unblinding.	This revision will allow greater flexibility when describing who may become unblinded to a single participant's treatment following an unblinding and allows the principal investigator, site personnel, and Sponsor personnel to conduct appropriate follow-up medical care for the participant once an emergency unblinding has taken place.
8.11 8.12	Compliance (Medication Adherence) Extent of Exposure	Updated the IV study treatment and overall study treatment (including oral step-down therapy) compliance definition and how exposures will be summarized.	It is clinically informative to know the compliance and extent of exposure for treated subjects. In addition, subjects overall study treatment exposure is an important criterion to evaluate the CE analysis population.
Global	Global	Minor editorial and document formatting revisions.	Minor syntax and grammar edits made for clarity and correctness.

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-7625A Plus Metronidazole versus Meropenem in Pediatric cIAI
Sponsor Product Identifiers	MK-7625A Ceftolozane/tazobactam
Trial Phase	2
Clinical Indication	Treatment of complicated intra-abdominal infection (cIAI)
Trial Type	Interventional
Type of control	Active control
Route of administration	Intravenous (IV) with optional oral step-down therapy
Trial Blinding	Double-blind
Treatment Groups	Subjects will be randomized to the experimental (ceftolozane/tazobactam + metronidazole) or comparator (meropenem + placebo) treatment arm to receive IV study treatment administered as a 60-minute (±10 minutes) infusion as follows: Group 1 (Ages 12 to <18 years, n≥50 combined with Group 2): Ceftolozane 1 g and tazobactam 0.5 g IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day) OR Meropenem 20 mg/kg (maximum 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours Group 2 (Ages 6 to <12 years, n≥50 combined with Group 1): Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day) OR Meropenem 20 mg/kg (maximum 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours Group 3 (Ages 2 to <6 years, n≥57 combined with same age group in MK-7625A-034: Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day) OR Meropenem 20 mg/kg (maximum 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours Group 4 (Ages 3 months to <2 years, n≥24 combined with same age group in MK-7625A-034: Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day) OR Meropenem 20 mg/kg (maximum 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours Group 5 (Ages birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months, n≥21 combined with same age group in MK-7625A-034:

	Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole IV every 8-12 hours (see below for metronidazole dosing for Group 5) OR Meropenem 20 mg/kg* (maximum 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours *NOTE: Some literature supports a higher meropenem dosage (up to 30 mg/kg every 8 hours) for subjects 14 days to <3 months of age; therefore, meropenem dosing up to 30 mg/kg every 8 hours may be used for subjects 14 days to <3 months of age at the investigator's discretion. <u>Metronidazole Dosing for Group 5</u> *Subjects >28 days of age:* Metronidazole 10 mg/kg every 8 hours (maximum dose 1.5 g/day) *For subjects ≤28 days of age the suggested dosing regimen is listed below; however, other site-specific standard of care metronidazole dosing may be used at the investigator's discretion.* *Subjects ≤28 days of age and ≤2 kg:* Metronidazole 15 mg/kg loading dose, then 7.5 mg/kg/dose every 12 hours *Subjects ≤28 days of age and >2 kg:* Metronidazole 15 mg/kg loading dose, 10 mg/kg dose every 8 hours NOTE: • Subjects 7 to 28 days of age who receive metronidazole with a frequency other than every 8 hours must receive placebo at the same frequency to maintain blinding. • In Ukraine, enrollment will be limited to subjects 2 years to < 18 years of age (Groups 1-3). Enrollment of subjects < 2 years old (Groups 4-5) is not applicable at Ukrainian study sites.
Number of trial subjects	Approximately 240 (combined across MK-7625A-034 and MK-7625A-035) subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 3 years from the time the first subject (or their legally acceptable representative) provides documented informed consent/assent until the last subject's last study-related contact.
Duration of Participation	Each subject will participate in the trial for approximately 5 to 7 weeks from the time the subject or subject's legal representative provides documented informed consent until the last subject's last study-related contact. After a screening phase of up to 48 hours, each subject will receive study treatment (IV only or IV + oral) for a minimum of 5 days to a maximum of 14 days. After the end of treatment, each subject enters a follow-up phase consisting of a Test of Cure (TOC) Visit 7 to 14 days after the last dose of study treatment and a Last Follow-up (LFU) Visit 21 to 28 days after the last dose of study treatment.

Randomization Ratio	3:1 for ceftolozane/tazobactam + metronidazole: meropenem + placebo

A list of abbreviations used in this document can be found in Appendix 12.3.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase 2 randomized, active comparator-controlled, multicenter, double-blind trial evaluating the safety and efficacy of ceftolozane/tazobactam (MK-7625A) plus metronidazole versus meropenem plus placebo in pediatric subjects from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age with complicated intra-abdominal infection (cIAI).

MK-7625A-034 is a companion Phase 2 randomized, double-blind trial of ceftolozane/tazobactam versus meropenem in pediatric subjects with cUTI; MK-7625A-034 and MK-7625A-035 will be pooled together for a combined safety database. Thus, approximately 240 subjects (combined across MK-7625A-034 and MK-7625A-035) will be stratified by age to receive study treatment. After minimum enrollment targets for each age group are met (202 subjects total), additional subjects (combined across MK-7625A-034 and MK-7625A-035) will be enrolled in any of the 5 age groups.

NOTE: Approximately 90% of the randomized population will consist of subjects with a diagnosis of complicated appendicitis.

In MK-7625A-035, subjects will be randomized in a 3:1 ratio to receive IV ceftolozane/tazobactam plus metronidazole or meropenem plus placebo. After receiving at least 9 doses of double-blind IV study treatment, subjects in either treatment arm may be switched to open-label, standard of care oral step-down antibiotic therapy at the investigator's discretion. Oral step-down therapy is considered study treatment. Recommendations for oral step-down therapy are provided in Section 5.2.2 – Optional Oral Step-down Therapy.

The total duration of study treatment (IV only or IV + oral) is a minimum of 5 days and a maximum of 14 days.

Subjects will be randomized to the experimental (ceftolozane/tazobactam + metronidazole) or comparator (meropenem + placebo) treatment arm to receive IV study treatment administered as a 60-minute (±10 minutes) infusion as follows:

Group 1 (Ages 12 to <18 years, n≥50 combined with Group 2):
Ceftolozane 1 g and tazobactam 0.5 g IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day)

OR

Meropenem 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours

Group 2 (Ages 6 to <12 years, n≥50 combined with Group 1):
Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day)

OR

Meropenem 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours

Group 3 (Ages 2 to <6 years, n≥57 combined with same age group in MK-7625A-034:
Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day)

OR

Meropenem 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours

Group 4 (Ages 3 months to <2 years, n≥24 combined with same age group in MK-7625A-034:
Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole 10 mg/kg IV every 8 hours (maximum dose 1.5 g/day)

OR

Meropenem 20 mg/kg (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours

Group 5 (Ages birth [>32 weeks gestational age and ≥7 days postnatal] to <3 months, n≥21 combined with same age group in MK-7625A-034:
Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose) IV every 8 hours and metronidazole IV every 8 to 12 hours (see Table 6 for metronidazole dosing in Group 5)

OR

Meropenem 20 mg/kg* (maximum of 1 g/dose) IV every 8 hours and placebo for metronidazole IV every 8 hours

*NOTE: There is literature that supports a higher meropenem dosage (up to 30 mg/kg every 8 hours) for subjects 14 days to <3 months of age. Therefore, meropenem dosing up to 30 mg/kg every 8 hours may be used for subjects 14 days to <3 months of age at the investigator's discretion.

NOTE:

- Subjects 7 to 28 days of age who receive metronidazole dosing with a frequency other than every 8 hours must receive placebo dosing at the same frequency to maintain blinding.

- In Ukraine, enrollment will be limited to subjects 2 years to < 18 years of age (Groups 1-3). Enrollment of subjects < 2 years old (Groups 4-5) is not applicable at Ukrainian study sites.

Clinical and microbiological assessments will be performed at the following visits:

- End of IV Treatment Visit (EOIV)
- End of Treatment Visit (EOT)
- Test of Cure Visit (TOC)

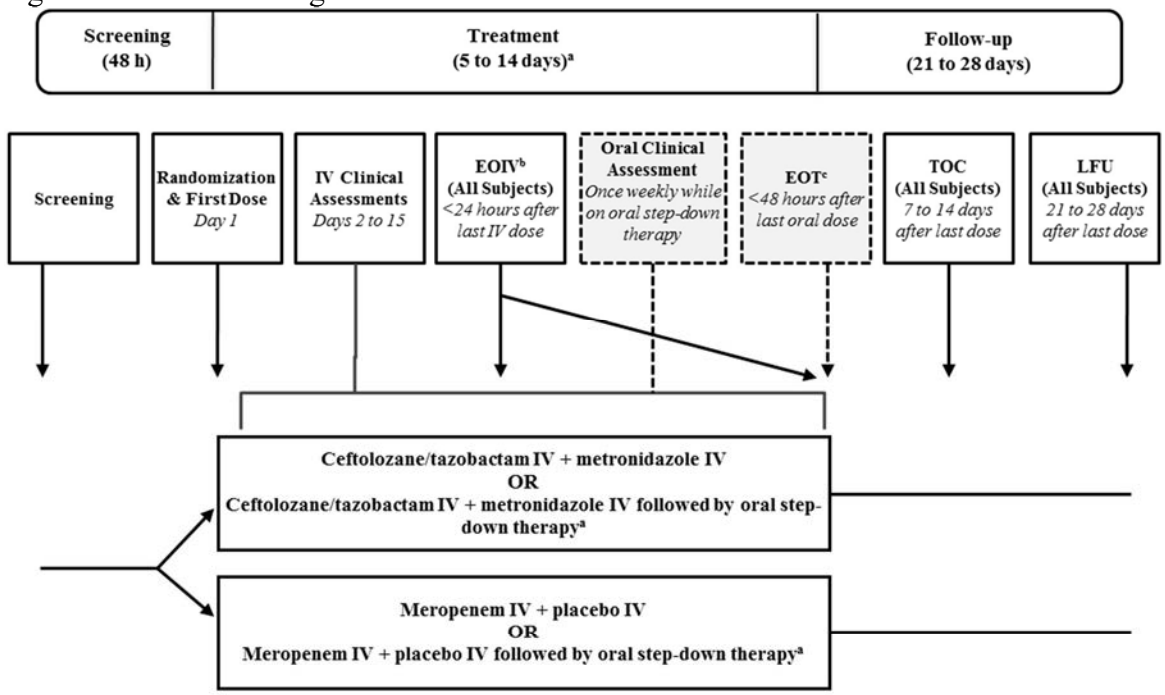
NOTE: For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate assessment does not need to be performed at the EOT Visit; the EOIV Visit will serve as the EOT Visit.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

Figure 1 Trial Diagram



EOIV = End of IV Treatment Visit; EOT = End of Treatment Visit; h = hours; IV = intravenous; LFU = Last Follow-up Visit; TOC = Test of Cure Visit
NOTE: See Section 6.0 – Trial Flow Chart for details.

a. After a minimum of 9 doses of double-blind IV study treatment, subjects may be switched to open-label, standard-of-care oral step-down antibiotic therapy at the discretion of the investigator. Total duration of study treatment (IV only or IV + oral) is a minimum of 5 days and a maximum of 14 days.
b. For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate EOT Visit for reassessment of clinical response is not required. For these subjects, the assessment of clinical response at the EOIV Visit will serve as the assessment of clinical response at EOT for analysis purposes.
c. For subjects who receive oral step-down therapy, a separate EOT Visit for reassessment of clinical response is required within 48 hours of the last dose of oral step-down therapy.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In male and female subjects from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cIAI:

3.1 Primary Objective(s) & Hypothesis(es)

To evaluate the safety and tolerability of ceftolozane/tazobactam plus metronidazole compared with that of meropenem

3.2 Secondary Objective(s) & Hypothesis(es)

1. To evaluate the efficacy of ceftolozane/tazobactam plus metronidazole compared with that of meropenem with respect to clinical response at the EOT and TOC Visits

2. To evaluate the efficacy of ceftolozane/tazobactam plus metronidazole compared with that of meropenem with respect to per-subject microbiological response at the EOT and TOC Visits

3.3 Exploratory Objectives

1. To evaluate the pharmacokinetics (PK) of ceftolozane and tazobactam
2. To evaluate the efficacy of ceftolozane/tazobactam plus metronidazole compared with that of meropenem with respect to clinical response at the EOIV Visit
3. To evaluate the efficacy of ceftolozane/tazobactam plus metronidazole compared with that of meropenem with respect to per-subject microbiological response at the EOIV Visit
4. To evaluate the efficacy of ceftolozane/tazobactam plus metronidazole compared with that of meropenem with respect to per-pathogen microbiological response at the EOIV, EOT, and TOC Visits

NOTE: For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate assessment does not need to be performed at the EOT Visit; the EOIV Visit will serve as the EOT Visit.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the IB/approved labeling for detailed background information on ceftolozane/tazobactam.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Ceftolozane/Tazobactam

Ceftolozane/tazobactam, a novel combination of ceftolozane and the β-lactamase inhibitor (BLI), tazobactam, is used to treat serious bacterial infections. Ceftolozane is a member of the cephalosporin class of antibiotics, which is well characterized in terms of safety, efficacy, and general antimicrobial profile. While ceftolozane alone represents an important therapeutic option for the treatment of infections caused by *Pseudomonas aeruginosa*, the efficacy of ceftolozane for the treatment of suspected gram-negative infections in general could be compromised by the spread of extended-spectrum β-lactamase (ESBL)-producing bacteria. Combining ceftolozane with a BLI, such as tazobactam, broadens its in vitro spectrum of activity to include many drug-resistant Enterobacteriaceae and is, thereby, likely to improve its clinical utility against gram-negative bacteria.

Ceftolozane (both alone and in combination with tazobactam) exhibits time-dependent killing activity against various gram-negative organisms, including drug-resistant *P. aeruginosa*. Ceftolozane/tazobactam has been shown to be active against strains of *P. aeruginosa* that are resistant to carbapenems, cephalosporins, fluoroquinolones, and/or aminoglycosides, including the majority of multidrug-resistant (MDR) isolates. The in vitro activity of

ceftolozane/tazobactam against the majority of ESBL-producing gram-negative bacilli and important anaerobic pathogens such as *Bacteroides fragilis* is greater than that of ceftolozane alone. Ceftolozane/tazobactam has no activity against enterococci and staphylococci.

Compared with other cephalosporins, ceftolozane requires a lower percentage of time above the minimum inhibitory concentration (T>MIC) of 8 µg/mL to achieve bacteriostasis (21% to 29%) or 1-log killing (27% to 35%) in animal models. Additionally, ceftolozane/tazobactam was superior to piperacillin/tazobactam against ESBL-producing *Escherichia coli* in a mouse sepsis model.

Clinical trials in adults have shown that the PK of ceftolozane/tazobactam is linear across a wide range of doses (up to 4.5 g [3 g ceftolozane/1.5 g tazobactam] as a single dose), distributes primarily to the extracellular fluid, has a relatively short terminal elimination half-life (approximately 2 to 3 hours for ceftolozane and 1 hour for tazobactam), and has low protein-binding (approximately 16% to 21% for ceftolozane and 30% for tazobactam). In adults, at the approved dose of 1.5 g, the mean (coefficient of variation [%CV]) values for area under the concentration-time curve (AUC) on Day 1 were 172 (14) and 24.4 (18) µg•h/mL for ceftolozane and tazobactam, respectively. The mean (%CV) values for maximum observed concentration (C_{max}) on Day 1 were 69.1 (11) and 18.4 (16) µg/mL for ceftolozane and tazobactam, respectively. As ceftolozane/tazobactam is primarily removed from the systemic circulation by renal excretion, dose adjustments are necessary in some subjects with renal impairment.

The safety and efficacy of ceftolozane/tazobactam was shown in Phase 3 trials in adult subjects with complicated urinary tract infections (cUTI) and cIAI. In these Phase 3 trials, the overall incidence of TEAEs was similar in the ceftolozane/tazobactam and comparator treatment arms. Ceftolozane/tazobactam was found to be noninferior to the comparator in these Phase 3 trials.

In summary, ceftolozane is a novel cephalosporin antibiotic that, in combination with a potent BLI, tazobactam, has broad-spectrum antibacterial coverage against Enterobacteriaceae, including ESBL-producing strains, and MDR *P. aeruginosa*. Ceftolozane/tazobactam is approved for use in adult patients with cUTI, including pyelonephritis, and cIAI (in combination with metronidazole) at a dose of 1.5 g (1 g ceftolozane/0.5 g tazobactam) every 8 hours. Both in vitro and in vivo safety and efficacy data support its continued clinical investigation in the pediatric population.

4.1.1.2 Complicated Intra-abdominal Infection

Uncomplicated IAI is characterized by involvement of a single infected abdominal organ without anatomical disruption; in contrast, cIAI is characterized by extension of infection into the peritoneal space, manifesting as abdominal abscess or diffuse peritonitis [1].

Primary peritonitis, defined as microbial infection of the peritoneum and peritoneal fluid without accompanying gastrointestinal (GI) or other visceral perforation, abscess or localized IAI, rarely develops in healthy adults but mainly occurs in infancy and early childhood and in adult cirrhotic patients [2]. Secondary peritonitis, the most common form of cIAI, typically

results from loss of integrity of the GI tract or infected viscera. Common causes of secondary bacterial peritonitis include penetrating or blunt abdominal trauma, appendicitis, diverticulitis, gastroduodenal ulcer perforation, biliary tract infections, and postoperative complications after abdominal procedures. Necrotizing enterocolitis (NEC), an inflammatory bowel necrosis that generally presents within the first 2 weeks of life and affects the terminal ileum, is the most common cause of secondary peritonitis in neonates [3]. In older pediatric patients, secondary peritonitis is predominantly associated with complicated appendicitis, although it also occurs as a result of intussusception, incarcerated hernia, volvulus, or rupture of a Meckel's diverticulum. In a study of community-acquired cIAI in pediatric patients aged from 1 month to 15 years, the vast majority of infections were complicated appendicitis (113/123, 92%) [4]. Complicated appendicitis arising from ruptured or gangrenous acute appendicitis is associated with significant increases in morbidity and length of hospitalization; perforation rates are as high as 82% for pediatric patients under 5 years and 100% for pediatric patients under 1 year [5].

The microbiology of cIAI is predominantly related to the site of loss of integrity within the GI tract and the level of disruption; as the lower GI tract contains hundreds of bacterial species at high concentrations, cIAI arising from the lower GI tract is likely to be polymicrobial in nature [6]. Infections derived from the colon are linked with facultative and obligate anaerobic organisms, gram-negative organisms (Enterobacteriaceae), other gram-negative bacilli and enterococci [6]. In a study of 100 pediatric patients with ruptured appendices, 144 aerobic isolates and 310 anaerobic isolates were detected, with the predominant aerobic bacteria being *E. coli*, alpha-hemolytic streptococci, gamma-hemolytic streptococci, group D enterococcus, and *P. aeruginosa*. Gram-negative bacilli (*Bacteroides fragilis* group and pigmented *Prevotella* and *Porphyromonas*), gram-positive anaerobic cocci, Fusobacterium spp, and *Clostridium spp* were the most common anaerobic isolates [7]. NEC is associated with fewer anaerobic isolates; aerobic species including *Klebsiella*, *Enterobacter* and *Streptococcus spp* are instead frequently reported.

Nosocomially-acquired pathogens associated with a high degree of antibiotic resistance include strains of *P. aeruginosa*, *S. marcescens*, Acinetobacter, and *Providencia spp*. Furthermore, drug-resistant pathogens such as ESBL-producing Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci may present in cIAI [8].

Intra-abdominal infection typically presents with acute onset abdominal pain associated with symptoms of gastrointestinal dysfunction such as anorexia, nausea or vomiting. In addition patients with cIAI will often display systemic signs of inflammation. A perforated viscera is likely to induce a systemic response, and such patients will often be febrile and tachycardic [9].

The treatment of cIAI involves a multifaceted approach including a source control procedure to drain infected foci and control ongoing peritoneal contamination as well as adjunctive antimicrobial treatment.

The importance of antimicrobial therapy selection has been highlighted in an analysis of clinical data generated in the Netherlands, which showed that hospitalized patients with

nosocomial cIAI who had not been administered appropriate therapy (16%) were at over 3-fold higher risk of clinical failure in relation to those that had. As a result, antimicrobial selection has significant implications in relation to both patient care and associated health care costs [2].

As cIAI is associated with mixed aerobic and anaerobic bacteria that act in synergy to increase pathogenicity, appropriate antimicrobial therapy should include either broad-spectrum agents or drug combinations to effectively combat infection. Thus, broad-spectrum empiric therapy of suspected or confirmed pediatric cIAI is indicated and treatment with carbapenems (imipenem or meropenem), piperacillin-tazobactam, ticarcillin-clavulanate, or an extended-spectrum cephalosporin (cefotoxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole is recommended [10].

4.1.2 Completed Preclinical and Clinical Trials of Ceftolozane/Tazobactam

Refer to the IB/approved labeling for detailed information on preclinical and completed clinical trials of ceftolozane/tazobactam.

The primary data supporting the efficacy of ceftolozane/tazobactam in the cIAI indication was derived from 2 large, identical, global, multicenter, randomized, double-blind, active-controlled Phase 3 trials (CXA-cIAI-10-08 [MK-7625A-003] and CXA-cIAI-10-09 [MK-7625A-004]). In both trials, adult subjects were randomized 1:1 to receive either IV ceftolozane/tazobactam 1.5 g (ceftolozane 1 g/tazobactam 0.5 g) every 8 hours plus metronidazole 500 mg every 8 hours or IV meropenem 1 g every 8 hours administered for 4 to 14 days. The results indicated that ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in the treatment of cIAI in adults.

In the treatment of adult subjects with nosocomial pneumonia (NP) (MK-7625A-008), ceftolozane/tazobactam 3 g (2 g ceftolozane and 1 g tazobactam) IV every 8 hours demonstrated noninferiority compared to meropenem 1 g IV every 8 hours for FDA and EMA primary and key secondary efficacy endpoints. Overall, both treatment groups demonstrated comparable per-pathogen clinical cure and microbiological eradication rates at the TOC visit against frequently isolated pathogens, including *P. aeruginosa*, Enterobacteriaceae, and *Haemophilus influenzae*.

The pediatric development program for ceftolozane/tazobactam included a pediatric PK and safety trial of ceftolozane/tazobactam, CXA-PEDS-13-08 (MK-7625A-010) [11]. This was a Phase 1, multicenter, single-dose, noncomparative, open-label trial in pediatric subjects with proven or suspected gram-negative infection or for peri-operative prophylaxis. This study had 6 age-based cohorts and enrolled a total of 43 subjects; 37 (86.0%) received study drug. Dose selections of ceftolozane/tazobactam for each age group (Group 1: ages ≥12 to <18 years, Group 2: ages ≥7 to <12 years, Group 3: ages ≥2 to <7 years, Group 4: ages ≥3 months to <2 years, Group 5: >32 weeks gestation, 7 days postnatal to <3 months, and Group 6: ≤32 weeks gestation, 7 days postnatal to <3 months) were projected to achieve exposures similar to those observed in adults who received the approved dose for cUTI and cIAI. Ceftolozane and tazobactam PK parameters were generally comparable across Groups 1 to 4 (ages 3 months to <18 years). Subjects in Groups 5 and 6 (birth [7 days postnatal] to <3 months of

age) had a lower CL than older children; however, there was no consistent trend in the weight-normalized CL across Groups 1 to 6. Data from MK-7625A-010 were used to determine appropriate doses for the present trial, as detailed in Section 4.2.2.1 – Rationale for Ceftolozane/Tazobactam Dosage.

Ceftolozane/tazobactam administered as a single, age-based dose was generally well tolerated in MK-7625A-010. Overall, 11 subjects (29.7%) experienced a total of 26 TEAEs. No severe TEAEs or TEAEs leading to discontinuation of study treatment were reported, and there were no deaths during the trial. Two subjects had nonserious treatment-related TEAEs (1 subject in Group 1 with dizziness and 1 subject in Group 3 [30/15 mg/kg dose] with bradycardia and tachycardia). Three subjects had SAEs (1 subject from Group 1 with pneumonia, 1 subject from Group 2 with infective pulmonary exacerbation of cystic fibrosis, and 1 subject from Group 4 [30/15 mg/kg dose] with device-related sepsis), which were all deemed unrelated to trial treatment. No subject in Groups 5 or 6 experienced a treatment-related TEAE or SAE. No clinically significant laboratory abnormalities or changes in electrocardiograms were observed after administration of ceftolozane/tazobactam.

4.1.3 Ongoing Clinical Trials of Ceftolozane/Tazobactam

Refer to the IB for detailed information for ongoing clinical trials of ceftolozane/tazobactam.

In addition to the present trial, the current clinical development program for ceftolozane/tazobactam includes 4 ongoing/planned clinical studies: 1) a Phase 3, randomized, double-blind, active comparator-controlled study comparing ceftolozane/tazobactam plus metronidazole versus meropenem in adult Chinese subjects with cIAI, 2) a Phase 2, randomized, double-blind, active comparator-controlled study comparing ceftolozane/tazobactam versus meropenem in pediatric subjects with cUTI, including pyelonephritis, 3) a Phase 1, open-label, noncomparative study evaluating the safety, tolerability, and PK of ceftolozane/tazobactam in pediatric subjects with NP, and 4) a Phase 1, non-randomized, single-arm, single-site, fixed-sequence open-label, PK, safety, and tolerability study of ceftolozane/tazobactam in healthy Chinese subjects.

4.1.4 Information on Other Trial-related Therapy

4.1.4.1 Comparator Therapy

Subjects in the comparator arm of the present trial will receive IV meropenem (Table 6). Meropenem is a carbapenem antibiotic indicated as single-agent therapy for the treatment of complicated appendicitis and peritonitis caused by viridans group streptococci, *E. coli, Klebsiella pneumoniae, P. aeruginosa, B. fragilis B. thetaiotaomicron, and Peptostreptococcus species*. See Section 4.2.2.3 – Rational for the Use of Comparator and Section 4.2.2.4 – Rationale for Comparator Dosage for additional details on the efficacy and safety of meropenem in the treatment of cIAI.

Meropenem exerts its bactericidal activity by inhibiting bacterial cell wall synthesis in gram-positive and gram-negative bacteria through binding to penicillin-binding–proteins. Like other β-lactam antibiotics, the T>MIC for meropenem has been shown to best correlate with efficacy. In preclinical models, meropenem demonstrated activity when plasma

concentrations exceeded the MIC of the infecting organisms for approximately 40% of the dosing interval.

4.1.4.2 Metronidazole for Adjunctive Anaerobic Coverage

Subjects in the ceftolozane/tazobactam arm of this trial will receive adjunctive therapy with IV metronidazole (Table 6).

Metronidazole injection, USP, is a parenteral formulation of the synthetic nitroimidazole antibacterial agent 2-methyl-5-nitro-1H-imidazole-1-ethanol.

The addition of metronidazole in combination with ceftolozane/tazobactam ensures coverage of intra-abdominal infections caused by anaerobic bacteria including Bacteroides species including the *B. fragilis* group (*B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B vulgatus*), Clostridium species, Eubacterium species, Peptococcus species, and Peptostreptococcus species.

Metronidazole is recommended as part of combination therapy for empiric treatment of cIAI in children in the Infectious Diseases Society of America (IDSA) guidelines on treatment of cIAI [1].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Clinical trials have indicated that ceftolozane is well tolerated and generally safe in healthy adult subjects, adult subjects with varying degrees of renal impairment, and adult subjects with cIAI or cUTI. The Phase 1 PK and safety trial in pediatric subjects (CXA-PEDS-13-08 [MK-7625A-010]; see Section 4.1.2 – Completed Preclinical and Clinical Trials of Ceftolozane/Tazobactam used an adaptive trial design wherein enrollment of Groups 1 to 4 (ages 3 months to <18 years) was conducted in parallel but enrollment of Groups 5 and 6 (ages birth to <3 months) did not begin until PK assessments and subject safety data from the older age groups were reviewed. Data from this trial revealed that ceftolozane/tazobactam doses resulting in exposures similar to those observed in adult subjects with cUTI or cIAI were safe and well tolerated in pediatric subjects.

The present trial (MK-7625A-035) will enroll pediatric subjects from birth to <18 years of age (from 2 years to < 18 years of age in Ukraine) who present with cIAI to establish the safety and efficacy of ceftolozane/tazobactam in this population. The pediatric dosing recommendations (see Section 4.2.2.1 – Rationale for Ceftolozane/Tazobactam Dosage for rationale for dose selection) were developed using data from subjects from birth (>32 weeks gestational age and ≥7 days postnatal) to <18 years of age; no data were available from subjects ≤32 weeks gestational age or <7 days postnatal to <3 months of age. Neonatal renal function is closely related to both gestational age and postnatal age. Because serum creatinine fluctuates in the first week of life, the revised Schwartz equation [12], which will be used to calculate renal function in this population, is not recommended for use until after the first

week of life. Therefore, the present trial defines "birth" as >32 weeks gestational age and ≥7 days postnatal.

Because ceftolozane/tazobactam was well tolerated in the Phase 1 pediatric PK and safety trial (CXA-PEDS-13-08 [MK-7625A-010]), parallel enrollment into active and comparator groups is considered appropriate for the present trial. Investigators, Sponsors, trial personnel, and subjects will all be blinded to prevent bias in treatment allocation and in the assessment of safety and efficacy. Likewise, randomization will be used to produce similar treatment arms and reduce bias.

4.2.1.1 Rationale for Sample Size

This trial is being conducted to establish the safety and tolerability of ceftolozane/tazobactam in pediatric subjects with cIAI. The efficacy of ceftolozane/tazobactam in pediatric subjects with cIAI may be extrapolated from the corresponding adult trials. Therefore, the calculation of cumulative sample size for this trial is based on obtaining sufficient data to evaluate the safety of this drug in pediatric subjects by combining safety data from the present trial and MK-7625A-034 (the companion trial in pediatric subjects with cUTI) (see Section 8.9—Sample Size and Power Calculations). Combining subjects across both studies is intended to provide flexibility and enable timely enrollment of the trials. In addition, a minimum enrollment target of at least 4 subjects in Groups 3-5 are in place to ensure data are obtained for these age groups from subjects with cIAI. This is an exploratory trial and is not powered to test formal hypotheses.

Approximately 240 subjects (combined across MK-7625A-034 and MK-7625A-035) will receive study treatment (approximately 180 ceftolozane/tazobactam-treated and 60 comparator-treated subjects). After the minimum enrollment targets for each age group are met (202 subjects total), additional subjects (combined across MK-7625A-034 and MK-7625A-035) will be enrolled in any of the 5 age groups.

4.2.2 Rationale for Dose Selection/Regimen

4.2.2.1 Rationale for Ceftolozane/Tazobactam Dosage

The proposed ceftolozane/tazobactam pediatric doses were projected using a population PK approach using data from 13 clinical studies (12 adult studies and 1 pediatric study). The PK analysis showed that 2-compartment models best described the concentration-time profiles of ceftolozane and tazobactam. The fit of the models was improved by including allometric scaling using body weight as a covariate on clearance (CL), central volume of distribution (Vc), peripheral volume of distribution (Vp), and intercompartmental clearance (Q, for tazobactam only). In the final models, renal function (estimated glomerular filtration rate [eGFR]) was included as a covariate on CL for ceftolozane. For tazobactam, presence of infection (as a categorical variable: Presence or absence) was also a significant covariate on CL for tazobactam. Tazobactam CL for subjects was estimated to be 67.7% of the CL for those without infection. Infection status did not appear to be a significant covariate on the PK of ceftolozane.

The final PK models for ceftolozane and tazobactam were used to simulate the AUC from 0 to 8 hours (AUC_{0-8}) and the C_{max} in pediatric subjects with infections on Day 3, which was shown to provide steady-state exposures. To provide a benchmark for evaluating the safety of ceftolozane and tazobactam in simulated pediatric subjects, Day 3 plasma exposure parameters for adult subjects were simulated. For predicting efficacy of the doses, probability of target attainment (PTA) after the first dose for adult subjects and 5 pediatric age groups was also simulated.

The criteria used in evaluating the appropriateness of doses were:

- The 95th percentile of pediatric ceftolozane and tazobactam exposures (AUC and C_{max}) on Day 3 not exceeding the corresponding 95th percentile of adult exposures; and

- The ceftolozane Day 1 PTA (initial dose) ≥90% based on concentrations exceeding an MIC of 4 µg/mL (the Clinical and Laboratory Standards Institute [CLSI] breakpoint) for at least 30% of the dosing interval and a tazobactam Day 1 PTA ≥90% based on concentrations exceeding a threshold concentration of 1 µg/mL for at least 20% of the dosing interval.

Similar to other β-lactams, the PK target that best correlates with in vivo efficacy for ceftolozane is the percentage of the dosing interval during which the free concentration of ceftolozane in plasma exceeds the MIC (% *f*T>MIC). A % *f*T>MIC of 30% was selected as the criterion because data from a neutropenic mouse thigh infection model showed that the % *f*T>MIC ranged from 26.7% to 35.3% for a 1-log kill [13]. The CLSI breakpoints are 2 µg/mL for Enterobacteriaceae and 4 µg/mL for *Pseudomonas aeruginosa*. The higher breakpoint of 4 µg/mL was chosen to ensure coverage for both organisms.

Because tazobactam does not have intrinsic antibacterial activity, an MIC cannot be determined. Instead, the threshold drug concentration (C_t) needed to effectively neutralize the β-lactamase enzyme produced by bacteria is used for target attainment [14]. Time above a C_t of 1 µg/mL for free tazobactam exposures of 20%, which is supported by data from a mouse model and clinical studies, was used.

Based on the exposure and PTA criteria described above, the simulations in pediatric subjects indicated that the following doses are appropriate for evaluation in this trial:

- 12 to <18 years of age: Ceftolozane 1 g with tazobactam 0.5 g via a 60-minute (±10 minutes) IV infusion every 8 hours
- <12 years of age: Ceftolozane 20 mg/kg with tazobactam 10 mg/kg via a 60-minute (±10 minutes) IV infusion every 8 hours (not to exceed a dose of ceftolozane 1 g and tazobactam 0.5 g)

The ceftolozane and tazobactam exposures and PTA for adult and pediatric subjects at these doses are summarized in Table 1 and Table 2, respectively. As shown in these tables, the selected doses provide exposures for the age groups that do not exceed the corresponding 95th percentile of adult exposures and achieve PTAs ≥90%.

Table 1 Ceftolozane Exposure and Target Attainment Summary for Simulated Adult and Pediatric Subjects

Parameter	Statistic	Adult Subjects (n=1000)	Pediatric Age Group[a]				
			1 1000 mg (n=1200)	2 20 mg/kg (n=1000)	3 20 mg/kg (n=1000)	4 20 mg/kg (n=1000)	5 20 mg/kg (n=1200)
Age (years)	Mean (SD)	53.57 (19.09)	15.00 (1.74)	9.52 (1.45)	4.51 (1.45)	0.80 (0.44)	0.13 (0.07)
	Median	56.00	14.99	9.53	4.53	0.71	0.12
	5th, 95th	22.0, 81.0	12.3, 17.7	7.3, 11.8	2.2, 6.7	0.3, 1.7	0.0, 0.2
AUC_{0-8} (µg × h/mL), Day 3	Mean (SD)	213.36 (171.91)	172.11 (78.76)	176.08 (69.92)	153.13 (60.32)	162.04 (63.15)	157.36 (65.19)
	Median	176.00	160.00	161.00	141.00	149.00	147.00
	5th, 95th	95.3, 388.0	73.2, 319.0	90.3, 315.0	77.0, 268.0	81.2, 276.5	71.3, 282.5
C_{max} (µg/mL), Day 3	Mean (SD)	69.66 (45.09)	86.04 (36.25)	92.68 (29.84)	82.37 (23.96)	74.37 (19.33)	62.06 (15.18)
	Median	56.10	80.35	86.90	79.35	72.40	60.15
	5th, 95th	32.9, 154.0	37.8, 154.0	53.1, 150.0	47.8, 125.0	45.9, 109.0	39.9, 89.4
Target attainment[b] Day 1	N (%)	1000 (100.0)	1188 (99.0)	995 (99.5)	992 (99.2)	1000 (100.0)	1196 (99.7)

5th, 95th = 5th, 95th percentiles; AUC_{0-8} = area under the concentration-time curve from time of drug administration (time 0) to 8 hours; C_{max} = maximum observed concentration; h = hours; N = number of subjects achieving target attainment; n = number of subjects; SD = standard deviation

[a] Age Group 1, 12 years ≤ age <18 years; Age Group 2, 7 years ≤ age < 12 years; Age Group 3, 2 years ≤ age <7 years; Age Group 4, 3 months ≤ age <2 years; Age Group 5, 7 days postnatal ≤ age <3 months.

[b] For ceftolozane, minimum effective concentration is 4 µg/mL and target is attainment of this concentration for 30% of the 8-hour dosing interval.

Table 2 Tazobactam Exposure and Target Attainment Summary for Simulated Adult and Pediatric Subjects

Parameter	Statistic	Adult Subjects (n= 1000)	Pediatric Age Group[a]				
			1 500 mg (n=1200)	2 10 mg/kg (n=1000)	3 10 mg/kg (n=1000)	4 10 mg/kg (n=1000)	5 10 mg/kg (n=1200)
Age (years)	Mean (SD)	46.37 (18.72)	15.00 (1.74)	9.52 (1.45)	4.51 (1.45)	0.80 (0.44)	0.13 (0.07)
	Median	44.00	14.99	9.53	4.53	0.71	0.12
	5th, 95th	20.0, 78.0	12.3, 17.7	7.3, 11.8	2.2, 6.7	0.3, 1.7	0.0, 0.2
AUC_{0-8} (µg × h/mL), Day 3	Mean (SD)	80.71 (148.87)	37.12 (23.29)	38.02 (24.49)	30.22 (19.18)	29.87 (19.05)	26.77 (16.50)
	Median	29.80	31.20	32.30	26.10	25.00	22.30
	5th, 95th	15.4, 379.0	12.4, 83.1	12.3, 84.5	10.2, 62.9	10.0, 63.5	8.4, 57.3
C_{max} (µg/mL), Day 3	Mean (SD)	30.30 (34.73)	27.92 (14.51)	29.19 (14.69)	24.04 (11.78)	21.69 (10.54)	18.37 (8.81)
	Median	17.70	24.75	26.45	21.80	19.50	16.80
	5th, 95th	10.3, 108.0	10.7, 54.6	11.7, 57.7	9.6, 46.1	8.5, 42.2	7.6, 35.2
Target attainment[b] Day 1	N (%)	1000 (100.0)	1169 (97.4)	978 (97.8)	950 (95.0)	958 (95.8)	1116 (93.0)

5th, 95th = 5th, 95th percentiles; AUC_{0-8}, area under the concentration-time curve from time of drug administration (time 0) to 8 hours; C_{max}, maximum observed concentration; N, number of subjects achieving target attainment; n, number of subjects; SD, standard deviation

[a] Age Group 1, 12 years ≤ age <18 years; Age Group 2, 7 years ≤ age < 12 years; Age Group 3, 2 years ≤ age <7 years; Age Group 4, 3 months ≤ age <2 years; Age Group 5, 7 days postnatal ≤ age <3 months.

[b] For tazobactam, threshold concentration is 1 µg/mL and target is attainment of this concentration for 20% of the 8-hour dosing interval.

Varying age-appropriate volumes of a fixed concentration of ceftolozane/tazobactam will be administered IV to achieve the intended dose in each pediatric subject. The same IV formulation will be used across all age groups.

4.2.2.2 Rationale for Metronidazole Dosage

Data on the PK and ideal dosing of metronidazole in pediatric patients are limited, especially for pediatric patients less than 1 month of age. As a result, dosing recommendations are highly variable without an accepted standard [15]. Suggested dosing recommendations for subjects <1 month old outlined in the protocol are based on one of the more frequently used dosing schedules [16]. However, to allow for potential variations in metronidazole dosing between different sites participating in this trial, the protocol allows for the use of site-specific standard of care dosing in subjects <1 month of age. Sites that use dosing schedules other than every 8 hours must adjust the blinding of placebo in subjects randomized to the meropenem arm.

In older pediatric patients, metronidazole dosing is more standardized. The dose of metronidazole for pediatric patients >1 month old chosen for this trial (30 mg/kg divided every 8 hours) is based on dosing recommendations from the IDSA guidelines on treatment of cIAI [1].

4.2.2.3 Rationale for the Use of Comparator

As described in Section 4.1.4.1 – Comparator Therapy, meropenem is indicated for treatment of IAI in adult and pediatric patients (3 months of age and older) caused by single or multiple bacteria sensitive to meropenem.

Meropenem is also one of several regimens recommended for empiric treatment of cIAI in pediatric patients by the Surgical Infection Society and IDSA current treatment guidelines [1] and there is significant clinical experience from both clinical trials and post-marketing data for the use of meropenem in the treatment of pediatric cIAI. It is the optimal choice of comparator for ceftolozane/tazobactam as the every 8-hour dosing interval facilitates blinding.

In addition, the use of meropenem in this trial will allow for an adequately sized safety database when data from this trial are pooled with the companion Phase 2 trial of ceftolozane/tazobactam in pediatric subjects with cUTI (MK-7625A-034), which also utilizes meropenem as the comparator (see Section 4.2.1.1 – Rationale for Sample Size). Available Phase 3 comparative safety data for ceftolozane/tazobactam versus meropenem from trials in adults with cIAI [1] will allow comparison of the safety profiles of ceftolozane/tazobactam and meropenem in pediatric and adult subjects.

4.2.2.4 Rationale for Comparator Dosage

The meropenem dose for Groups 1 through 4 (20 mg/kg IV every 8 hours [maximum of 1 g/dose]) was chosen for this trial based on the approved dosage regimen for the treatment of cIAI [17].

Safety and efficacy data of meropenem in pediatric patients under 3 months of age are limited, and the optimal dose regimen for this age group has not been identified. However, a trial in 200 critically ill preterm and term infants (<91 days of age) with suspected or confirmed IAI showed that meropenem was safe and well tolerated at the 20 mg/kg dose [15]. Limited data on the PK of meropenem suggest that drug disposition in young infants may differ significantly from that in adults, likely related to developmental differences in renal function and differences in body composition seen in young infants. As a result, some sources recommend higher meropenem doses (up to 30 mg/kg IV every 8 hours) for the treatment of serious infections in neonates [18]. To accommodate potential variations in standard of care dosing, the protocol allows for a range of weight-based dosing schemes between 20 mg/kg and 30 mg/kg for subjects in Group 5 (birth [defined as >32 weeks gestational age and ≥7 days postnatal] to <3 months of age).

To ensure blinding, each dose of meropenem will be administered as a 60-minute (±10 minutes) infusion (versus the 30-minute infusion noted in the prescribing information) [17] to match the duration of infusion of ceftolozane/tazobactam. As described in Section 4.1.4 – Information on Other Trial-related Therapy, the efficacy of meropenem, like other β-lactam antibiotics, is dependent on the T>MIC of the pathogens being treated. Therefore, the efficacy of meropenem is not affected by prolonging the infusion. In addition, infusions of meropenem longer than 1 hour have been administered to patients with satisfactory results and without additional safety or tolerability risk [19].

Therefore, the Sponsor believes the dosage regimen of meropenem in this trial is a clinically appropriate and acceptable comparator with which to evaluate the safety and efficacy of ceftolozane/tazobactam in pediatric cIAI.

4.2.2.5 Rationale for Duration of Therapy and Optional Oral Step-Down Antibiotic Therapy

Current guidelines for the treatment of cIAI recommend 4 to 7 days of antibiotic therapy after adequate source control is achieved [1]. However, some types of pediatric cIAI, such as NEC, may require a longer duration of therapy of up to 14 days. Because subjects may be enrolled and started on study treatment before adequate source control is achieved and because some types of pediatric cIAI may require longer treatment courses, subjects in the present trial will receive 5 to 14 days of IV study treatment.

After receiving at least 9 doses of IV study treatment, subjects may be switched to oral step-down therapy at the investigator's discretion based on the subject's clinical condition (Section 5.2.2 – Optional Oral Step-down Therapy). The requirement of 72 hours (9 doses) of IV study treatment allows for evaluation of the safety, efficacy, and PK of ceftolozane/tazobactam while minimizing the need for prolonged hospitalization and IV access.

4.2.3 Rationale for Endpoints

4.2.3.1 Rationale for Safety Endpoints

To evaluate the safety and tolerability of ceftolozane/tazobactam in pediatric subjects, the incidence, severity, and type of AEs will be tabulated (see Section 7.2 – Assessing and Recording Adverse Events).

Laboratory data will be summarized by the type of laboratory test. Descriptive statistics of temperature, heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled timepoint.

Subjects may be asked to return for unscheduled visits in order to perform additional safety monitoring.

See Section 8.4.1 – Safety Endpoints for details about the analysis of safety endpoints and Section 8.5.1 – Efficacy Endpoints for details about the safety analysis population.

4.2.3.2 Rationale for Efficacy Endpoints

Because the mechanism of action and the potency of ceftolozane/tazobactam should be the same across all ages, adult and pediatric PK data can be compared to extrapolate the efficacy of ceftolozane/tazobactam from adult subjects to pediatric subjects. Therefore, efficacy is evaluated as secondary and exploratory objectives in this trial. There are no prespecified statistical hypotheses for this trial. The trial is not powered to statistically compare the efficacy of ceftolozane/tazobactam versus meropenem.

The secondary efficacy endpoints are:

- Clinical success rate at the EOT and TOC Visits, defined as the proportion of subjects in the analysis population who have a clinical response of cure.

- Per-subject microbiological success rate at the EOT and TOC Visits, defined as the proportion of subjects in the analysis population who have microbiological eradication or presumed eradication of all baseline pathogens.

The exploratory efficacy endpoints are:

- Clinical success rate at the EOIV Visit, defined as the proportion of subjects in the analysis population who have a clinical response of cure or partial improvement.

  NOTE: At EOIV, clinical success is defined as cure or partial improvement. At EOT and TOC, clinical success is defined as cure. The definition for clinical success at the EOIV Visit includes partial improvement to accommodate those subjects with partial improvement who are switched to oral step-down therapy at this time point.

- Per-subject microbiological success rate at the EOIV Visit, defined as the proportion of subjects in the analysis population who have a microbiological outcome of eradication or presumed eradication of all baseline pathogens.

- Per-pathogen microbiological success rate at the EOIV, EOT, and TOC Visits, defined as the proportion of baseline pathogens that have an outcome of microbiological eradication or presumed eradication.

NOTE: For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate assessment does not need to be performed at the EOT Visit; the EOIV Visit will serve as the EOT Visit.

4.2.3.2.1 Clinical Outcome

Investigators will determine clinical outcomes at the EOIV, EOT, and TOC Visits according to the definitions in Table 3. Subjects with failure or indeterminate outcomes will be considered to have an unfavorable clinical response.

For subjects who receive only IV study treatment and are not switched to oral step-down therapy, the EOIV assessment serves as the EOT assessment and these subjects do not have a separate EOT assessment. Subjects who are switched to oral step-down therapy will have both an EOIV and EOT assessment.

At EOIV, clinical success is defined as cure or partial improvement. At EOT and TOC, clinical success is defined as cure. Subjects with failure or indeterminate clinical outcomes will be considered to have an unfavorable clinical response.

Failure will be carried forward; subjects who are assessed as a failure before the TOC Visit should have “failure” recorded on the TOC Visit electronic case report form (eCRF). These subjects should attend the TOC Visit but will not have a new clinical outcome assessment at this visit.

Subjects who discontinue IV study treatment or discontinue from the trial prior to receiving 9 doses of IV study treatment for reasons other than those meeting the definition of failure will be assessed with a clinical outcome of indeterminate. See also Section 5.8 – Subject Withdrawal/Discontinuation Criteria, Section 7.1.4.1 – Withdrawal/Discontinuation, and Section 7.1.5.9 – Subjects Who Prematurely Discontinue From Study Treatment or the Trial.

Table 3 Clinical Outcome Categories

Outcome	Definition
Cure	Complete resolution or marked improvement in signs and symptoms of the cIAI or return to preinfection signs and symptoms such that no further antibiotic therapy (IV or oral) or surgical or drainage procedure is required for treatment of the cIAI.
Partial improvement (only at the EOIV Visit for subjects who switch to oral step-down therapy)	Partial resolution of signs and symptoms of the cIAI such that no further IV antibiotic therapy is required for the treatment of the cIAI; however, additional oral step-down therapy is required.
Failure	Any of the following is considered a clinical outcome of failure: • Requirement of antibiotic therapy beyond the protocol-defined treatment duration of 14 days. • Persisting or recurrent infection within the abdomen requiring additional intervention, including nonstudy antibiotics or repeat surgical intervention. NOTE: 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 treatment 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. • Post-surgical wound infection with signs of local infection, such as purulent exudate, erythema, or warmth that requires additional antimicrobial therapy and/or nonroutine wound care. • Death related to IAI
Indeterminate	Trial data are not available for evaluation of efficacy for any reason, including death during the trial period unrelated to the cIAI or extenuating circumstances which preclude classification as cure, partial improvement, or failure (eg, subject is lost to follow-up).

cIAI = complicated intra-abdominal infection; EOIV = End of IV Treatment; IV = intravenous

4.2.3.2.2 Microbiological Outcome

All microbiological outcomes will be based on laboratory results and determined by the Sponsor. Investigators are not responsible for assessment of microbiological outcomes.

Per-subject Microbiological Outcome

An overall microbiological response will be determined for each subject based on the individual microbiological response for each baseline pathogen. Microbiological response categories are eradication, presumed eradication, persistence, presumed persistence, persistence acquiring resistance, and indeterminate as defined in Table 4. Eradication or presumed eradication will be considered favorable microbiological responses; in order for the subject to have a favorable overall microbiological response (ie, eradication or presumed eradication), each baseline pathogen must have a favorable microbiological outcome.

Per-pathogen Microbiological Outcome

The per-pathogen microbiological outcome will be determined for each baseline infecting pathogen isolated by the Sponsor (see Table 4). Eradication or presumed eradication will be considered favorable microbiological responses.

Table 4 Microbiological Outcome Categories

Outcome[a]	Definition[a]
Eradication[b]	Absence of the baseline pathogen(s) in a postbaseline specimen appropriately obtained from the original site of infection.
Presumed eradication[b]	Absence of material to culture in a subject who is assessed as having partial improvement, or clinical cure.
Persistence	Presence of the baseline pathogen(s) in an appropriately obtained postbaseline specimen from the site of infection or surgical wound. NOTE: Cultures from indwelling drains are not considered appropriate.
Presumed persistence	Absence of material to culture in a subject who is assessed as a clinical failure.
Persistence acquiring resistance	Presence of baseline pathogen(s) in an appropriately obtained postbaseline specimen where the baseline pathogen(s) was susceptible to study treatment pretreatment and is resistant to study treatment post-treatment.
Indeterminate	• Baseline culture either not obtained or has no growth. • Postbaseline culture was not obtained and clinical assessment was not possible. • Any other circumstance that makes it impossible to define the microbiological response (eg, subject lost to follow-up).

[a] The per-pathogen microbiological outcome will be determined for each baseline infecting pathogen isolated by the Sponsor.

[b] Eradication or presumed eradication will be considered favorable microbiological responses.

Emergent Infection

Pathogens isolated after baseline will be assessed for the outcome of superinfection or new infection, as defined in Table 5.

Table 5 Emergent Infection Categories

Outcome	Definition
Superinfection	Isolation of a pathogen, other than the original baseline pathogen(s), from an appropriately obtained postbaseline specimen in a subject **while on study treatment.**
New infection	Isolation of a pathogen, other than the original baseline pathogen(s), from an appropriately obtained postbaseline specimen in a subject **after administration of the last dose of study treatment and through the TOC visit.**

See Section 8.4.2 - Efficacy Endpoints for details about efficacy analyses and Section 8.5.2 – Efficacy Analysis Populations for details about the efficacy analysis populations.

4.2.3.3 Rationale for Pharmacokinetic Endpoints

Whole blood samples (250 µL) will be collected at the time points specified in Section 6.0 – Trial Flow Chart for determination of plasma concentrations of ceftolozane, tazobactam, and tazobactam M1. Specific information about PK sample collection is provided in Section 7.1.3.6 – Pharmacokinetic Evaluations. These samples will provide pediatric PK data in the target population and will support further evaluation of the PK profiles of ceftolozane and tazobactam by confirming whether subjects achieve percentage of dosing interval during which free concentration of drug (ceftolozane) exceeds the MIC (%$fT>MIC$) of at least 30% (for an MIC of 4 µg/mL) for ceftolozane and percentage of dosing interval during which free concentration of drug (tazobactam) exceeds the Ct (%$fT>C_t$) of at least 20% (for a threshold concentration of 1 µg/mL) for tazobactam.

Pharmacokinetic data may also aid in the assessment of the clinical relationship between ceftolozane and tazobactam plasma concentrations and efficacy in the pediatric population.

See Section 8.4.3 – Pharmacokinetic Endpoints for details about analysis of PK endpoints.

4.3 Benefit/Risk

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

This trial will include pediatric subjects who require IV antibiotics for treatment of cIAI. If randomized to receive ceftolozane/tazobactam + metronidazole, subjects will receive an antibiotic regimen that is active against organisms frequently isolated from pediatric patients with cIAI and that has proven to be effective in large-scale clinical trials for the treatment of cIAI in adults (Section 4.1.1.1 – Ceftolozane/Tazobactam). Subjects who are randomized to the comparator arm will receive meropenem, an antibacterial agent approved for treatment of cIAI in pediatric patients 3 months of age and older and adults (Section 4.1.4.1 – Comparator Therapy).

Although potentially more frequent than the standard of care, the planned study procedures (see Section 6.0 – Trial Flow Chart) are generally typical procedures performed for this patient population. Trial procedures, including the number of blood draws for PK sampling, are limited in order to minimize risk. Additional burden may be incurred due to visits after release from the hospital; however, the procedures performed at these visits are generally not likely to lead to significant harm (eg, blood draws, physical examinations, vital signs) and are necessary to support a robust evaluation of the safety and efficacy of the investigational drug.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying ceftolozane/tazobactam IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age with cIAI will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have a legally acceptable representative who provides documented informed consent/assent for the trial.
2. Be a male or female from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age.

   NOTE: In Ukraine, enrollment age of a male or female subject will be limited to 2 years to < 18 years (Groups 1-3). Subjects < 2 years old (Groups 4-5) are not permitted to enroll into the study at Ukrainian sites.
3. Be able to comply with the protocol for the duration of the trial.
4. Require IV antibacterial therapy for the treatment of presumed or documented cIAI as demonstrated by either:

   Operative diagnosis (laparotomy, laparoscopy or percutaneous drainage) of cIAI, defined as evidence of infection within the abdominal cavity extending beyond the hollow viscus of origin into the peritoneal space as demonstrated by either abscess formation or peritonitis.

   OR

   Preoperative diagnosis of cIAI, defined as meeting both of the criteria below:

   a) Clinical evidence of cIAI as indicated by one or more systemic signs or symptoms that accompany cIAI, such as fever, leukocytosis, hypotension,

abdominal pain, nausea/vomiting, anorexia, abdominal mass on clinical examination, or altered mental status.

b) Radiographic evidence consistent with cIAI.

NOTE: Approximately 90% of the randomized population will consist of subjects with a diagnosis of complicated appendicitis.

5. Have an operative procedure for the current diagnosis and management of cIAI planned or completed within 24 hours of the first dose of an antibacterial drug.

   NOTE: Subjects with a diagnosis of NEC are exempt from this inclusion criteria and are not required to have surgery planned or completed in order to be eligible for enrollment.

6. Have baseline intra-abdominal specimen collection in compliance with Section 7.1.3.4 – Intra-abdominal Samples for Culture. Subjects enrolled preprocedure should have a sample obtained during the interventional procedure performed to comply with Section 7.1.3.4.

   NOTE: Subjects with NEC that do not require surgical intervention are exempt from this inclusion criteria and are not required to have an intra-abdominal culture.

7. Meet one of the following categories:

   a) The subject is a male who is not of reproductive potential, defined as a male who has azoospermia (whether due to being prepubertal, having had a vasectomy, or an underlying medical condition).

   b) The subject is a female not of reproductive potential, defined as a female who either: (1) Has not undergone menarche, (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening, or (3) has a congenital or acquired condition that prevents childbearing.

   c) The subject is a female or a male of reproductive potential who agrees to avoid becoming pregnant or impregnating a partner during screening, while receiving study treatment and for at least 30 days after the last dose of study treatment by complying with one of the following: (1) Practice abstinence[a] from heterosexual activity OR (2) use (or have their partner use) acceptable contraception during heterosexual activity.

   Acceptable methods of contraception are[b]:

   Single method (1 of the following is acceptable):

   - Intrauterine device
   - Vasectomy of a female subject's male partner
   - Contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous females only)
- Contraceptive sponge (nulliparous females only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: Oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[a] Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently used as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

[b] If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

8. Meet the following criteria for a female subject who is of reproductive potential:

a) The subject is not pregnant (as confirmed by serum pregnancy test at screening) and not planning to become pregnant within 30 days of the last day of treatment administration,

AND

b) The subject is nonlactating

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 30 days prior to the first dose of study treatment in this current trial.
2. Has previously participated in any trial of ceftolozane or ceftolozane/tazobactam or has enrolled previously in the current trial and been discontinued.
3. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that, in the opinion of the investigator, might expose the subject to increased risk by participating in the trial, confound the results of the trial, or interfere with the subject's participation for the full duration of the trial.

4. Has a history of any moderate or severe hypersensitivity (eg, anaphylaxis), allergic reaction, or other contraindication to any of the following: β-lactam antibiotics (eg, penicillins, cephalosporins, and carbapenems), β-lactamase inhibitors (eg, tazobactam, sulbactam, clavulanic acid, avibactam), or metronidazole.

   NOTE: A history of mild rash to any of these agents is not a contraindication to enrollment.

5. Has an IAI within the past 1 year prior to randomization known to be caused by a pathogen resistant to either IV study treatment.

6. Has a concomitant infection at the time of randomization that requires nonstudy systemic antibacterial therapy in addition to IV study treatment or oral step-down therapy (medications with only gram-positive activity [eg, vancomycin, linezolid] are allowed).

7. Has received potentially therapeutic antibacterial therapy (eg, with gram-negative activity) for a duration more than 24 hours during the 48 hours preceding the first dose of study treatment, unless the subject is considered to be failing antibiotic therapy for cIAI.

   NOTE: A subject considered to be failing a previous antibiotic regimen must meet all of the following criteria:

   a) Has received the systemic antibacterial treatment for at least 48 hours
   b) Has clinical and operative or radiographic findings clearly indicating ongoing infection
   c) Has planned operative intervention no more than 24 hours after first dose of study treatment
   d) Has not received any further nonstudy antibiotics postoperatively

8. Has any of the following:

   a) Intractable cIAI that the investigator anticipates would require more than 14 days of study treatment
   b) Abdominal wall abscess
   c) Small bowel obstruction
   d) Ischemic bowel disease without perforation
   e) Traumatic bowel perforation with surgery within 12 hours of perforation
   f) Perforation of gastroduodenal ulcers requiring surgery within 24 hours of perforation (these are considered situations of peritoneal soiling before the infection has become established)
   g) Suspected uncomplicated intra-abdominal infection (eg, cholecystitis without rupture or extension beyond the gallbladder wall)
   h) Acute suppurative cholangitis
   i) Infected necrotizing pancreatitis

j) Pancreatic abscess

9. Has moderate or severe impairment of renal function, defined as an estimated creatinine clearance (CrCL) <50 mL/min/1.73 m^2 based on the revised Schwartz equation [12] or requirement for peritoneal dialysis, hemodialysis, or hemofiltration.

10. Has one or more of the following laboratory abnormalities in a specimen obtained at baseline:

    a) Absolute neutrophil count (ANC) <1000/mm^3

    b) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × the upper limit of normal (ULN)

    c) Total bilirubin ≥2 × ULN (if 7 to ≤28 days of age and breastfeeding, total bilirubin >10 mg/dL OR ≥2 × ULN)

11. Has a seizure disorder or is anticipated to be treated with divalproex sodium or valproic acid during the course of study treatment.

12. Is receiving, or is expected to receive, any of the following medications:

    a) Immunosuppressive agents

       NOTE: 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.

    b) Probenecid

    c) Valproic acid or divalproex sodium

    d) Disulfiram

    e) Ergot derivatives

    f) Ethanol-containing medications

    g) Nonstudy systemic (IV or oral) antibacterial treatments

       NOTE: Subjects who require empiric enterococcal coverage for the index cIAI may receive concomitant therapy with an enterococcal antibiotic with activity limited to gram-positive coverage (eg, vancomycin, daptomycin, teicoplanin, linezolid). One dose of prophylactic antibiotic with gram-negative activity is allowed.

       Subjects who require empiric antifungal coverage for the index cIAI may receive concomitant antifungal coverage with an azole, echinocandin, or polyene antifungal as chosen by the investigator based on local standard of care.

13. Has any rapidly progressing disease or immediately life-threatening illness, including acute hepatic failure, respiratory failure, or septic shock.

14. Has an immunocompromising condition, including established acquired immune deficiency syndrome (AIDS), hematological malignancy, or bone marrow transplantation, or is receiving immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, or

chronic administration of systemic corticosteroids (defined as the systemic equivalent of ≥2 mg/kg total daily dose of prednisone for participants ≤20 kg, or >40 mg of prednisone per day for participants >20 kg, administered continuously for more than 14 days in the 30 days prior to the first dose of ceftolozane/tazobactam).

15. Has a history of malignancy ≤5 years prior to providing documented informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
16. Planned receipt of suppressive/prophylactic antibiotics with gram-negative activity after completion of study treatment.
17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 6 and Table 7.

5.2.1 Intravenous Trial Treatments

The IV treatment regimens to be used in this trial are outlined in Table 6.

After receiving at least 9 doses of double-blind IV study treatment, subjects in either treatment arm may be switched to open-label, standard of care oral step-down antibiotic therapy at the investigator's discretion (Section 5.2.2 – Optional Oral Step-down Therapy). Total antibiotic duration (IV only or IV + oral) is a minimum of 5 days and a maximum of 14 days.

NOTE: In Ukraine, enrollment will be limited to subjects 2 years to < 18 years of age (Groups 1-3). Study treatments for Groups 4 and 5 are not applicable at Ukrainian sites.

Table 6 Intravenous Trial Treatments

Drug	Dose/Potency	Dose Frequency[a]	Route of Administration[b]	Treatment Period[b]	Use
Group 1 (12 to <18 years [n≥50 combined with Group 2])[c]					
Ceftolozane/ tazobactam	Ceftolozane 1 g and tazobactam 0.5 g	Every 8 hours	IV	5-14 days	Experimental
Metronidazole	Metronidazole 10 mg/kg (maximum dose 1.5 g/day)	Every 8 hours	IV	5-14 days	Adjunctive
Meropenem and placebo for metronidazole	Meropenem 20 mg/kg (maximum 1 g/dose)	Every 8 hours	IV	5-14 days	Active comparator

Drug	Dose/Potency	Dose Frequency[a]	Route of Administration[b]	Treatment Period[b]	Use
Group 2 (6 to <12 years [n≥50 combined with Group 1])[c]					
Ceftolozane/ tazobactam	Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose)	Every 8 hours	IV	5-14 days	Experimental
Metronidazole	Metronidazole 10 mg/kg (maximum dose 1.5 g/day)	Every 8 hours	IV	5-14 days	Adjunctive
Meropenem and placebo for metronidazole	Meropenem 20 mg/kg (maximum 1 g/dose)	Every 8 hours	IV	5-14 days	Active comparator
Group 3 (2 to <6 years [n≥57 combined with same age group in MK-7625A-034])[c]					
Ceftolozane/ tazobactam	Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose)	Every 8 hours	IV	5-14 days	Experimental
Metronidazole	Metronidazole 10 mg/kg (maximum dose 1.5 g/day)	Every 8 hours	IV	5-14 days	Adjunctive
Meropenem and placebo for metronidazole	Meropenem 20 mg/kg (maximum 1 g/dose)	Every 8 hours	IV	5-14 days	Active comparator
Group 4 (3 months to <2 years [n≥24 combined with same age group in MK-7625A-034])[c]					
Ceftolozane/ tazobactam	Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose)	Every 8 hours	IV	5-14 days	Experimental
Metronidazole	Metronidazole 10 mg/kg (maximum dose 1.5 g/day)	Every 8 hours	IV	5-14 days	Adjunctive

Drug	Dose/Potency	Dose Frequency[a]	Route of Administration[b]	Treatment Period[b]	Use
Meropenem and placebo for metronidazole	Meropenem 20 mg/kg (maximum 1 g/dose)	Every 8 hours	IV	5-14 days	Active comparator
Group 5 (Birth[d] to <3 months [n≥21 combined with same age group in MK-7625A-034])[c]					
Ceftolozane/ tazobactam	Ceftolozane 20 mg/kg and tazobactam 10 mg/kg (maximum ceftolozane 1 g and tazobactam 0.5 g/dose)	Every 8 hours	IV	5-14 days	Experimental
Metronidazole	*Subjects >28 days of age:* Metronidazole 10 mg/kg every 8 hours (maximum dose 1.5 g/day) *For subjects ≤28 days of age, the suggested dosing regimen is listed below; however, other site-specific standard of care metronidazole dosing may be used at the investigator's discretion.* *Subjects ≤28 days of age and ≤2 kg:* Metronidazole 15 mg/kg loading dose, then 7.5 mg/kg/dose every 12 hours *Subjects ≤28 days of age and >2 kg:* Metronidazole 15 mg/kg loading dose, 10 mg/kg dose every 8 hours	Every 8-12 hours[f]	IV	5-14 days	Adjunctive
Meropenem and placebo for metronidazole[f]	Meropenem 20 mg/kg (maximum 1 g/dose)[e]	Every 8 hours	IV	5-14 days	Active comparator

Drug	Dose/Potency	Dose Frequency[a]	Route of Administration[b]	Treatment Period[b]	Use

IV = intravenous

[a] Each dose of ceftolozane/tazobactam or metronidazole or meropenem or placebo is administered as a 60-minute (±10 minutes) infusion. Ceftolozane/tazobactam plus metronidazole or meropenem plus placebo are to be dosed every 8 hours (±1 hour) after the previous infusion. The second IV dose has a ±4-hour window for dosing to facilitate adjustment of the dosing schedule (once every 8 hours) to be carried out throughout the dosing period.

[b] After receiving at least 9 doses of double-blind IV study treatment, subjects may be switched to open-label, standard of care, oral step-down therapy at the investigator's discretion. The total duration of study treatment (IV only or IV + oral) is a minimum of 5 days and a maximum of 14 days.

[c] The total minimum number of subjects in the 5 age groups combined across MK-7625A-034 and MK-7625A-035 is 202. After the minimum enrollment targets for each age group are met, additional subjects (combined across MK-7625A-034 and MK-7625A-035) will be enrolled in any of the 5 age groups.

[d] Birth is defined as >32 weeks gestational age and ≥7 days postnatal.

[e] Some literature supports a higher meropenem dosage (up to 30 mg/kg every 8 hours) for subjects 14 days to <3 months of age; therefore, meropenem dosing up to 30 mg/kg every 8 hours may be used for subjects 14 days to <3 months of age at the investigator's discretion.

[f] Subjects 7 to 28 days of age who receive metronidazole with a frequency other than every 8 hours must receive placebo at the same frequency to maintain blinding.

5.2.2 Optional Oral Step-down Therapy

After receiving at least 9 doses of double-blind, IV study treatment, subjects may be switched to open-label, standard of care, oral step-down antibiotic therapy at the investigator's discretion. Total antibiotic duration (IV only or IV + oral) is a minimum of 5 days to a maximum of 14 days. Optional oral step-down therapy is considered study treatment in this trial.

Oral step-down therapy should be guided by culture results and consistent with the local standard of care. Table 7 lists recommended options for oral step-down therapy.

Table 7 Recommended Oral Step-down Therapy Options

Antibiotic or Antibiotic Class[a]
β-lactam/β-lactamase inhibitor combination
Second or third generation cephalosporin in combination with metronidazole
Quinolone (if ciprofloxacin or levofloxacin are chosen, it should be used in combination with metronidazole)

[a] The choice of oral step-down therapy should be guided by culture results and based on local antibiotic susceptibility patterns.

NOTE: Regimens not listed above must be approved by the Sponsor.

5.2.3 Trial Treatments: Administrative Considerations

Trial treatment should begin as soon as possible after randomization and at the latest within 24 hours of randomization. There should be no medically inappropriate delay in randomization and subsequent study treatment.

All supplies indicated in Table 6 and Table 7 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.4 Dose Selection

5.2.4.1 Dose Selection (Preparation)

The following doses are to be used in this trial:

- 12 to <18 years of age: Ceftolozane 1 g with tazobactam 0.5 g via a 60-minute (±10 minutes) IV infusion every 8 hours
- <12 years of age: Ceftolozane 20 mg/kg with tazobactam 10 mg/kg via a 60-minute (±10 minutes) IV infusion every 8 hours (not to exceed a dose of ceftolozane 1 g and tazobactam 0.5 g)

The rationale for selection of doses to be used in this trial is provided in Section 4.2.2 – Rationale for Dose Selection/Regimen. The dosing calculations and drug preparation are described in detail in the pharmacy manual.

5.2.5 Timing of Dose Administration

Ceftolozane/tazobactam plus metronidazole or meropenem plus placebo are to be dosed every 8 hours* (±1 hour) after the previous infusion. The second IV dose has a ±4-hour window for dosing to facilitate adjustment of the dosing schedule (once every 8 hours) to be carried out throughout the IV dosing period. The final day of study treatment may extend into Day 15 to accommodate different start and stop times of the IV study treatment and/or dosing schedules of the oral step-down therapy.

*Subjects who are 7-28 days old may be dosed every 12 hours with metronidazole. Please refer to Table 6 in Section 5.2.1 – Intravenous Trial Treatments for metronidazole dosing recommendations in this age group.

5.2.6 Trial Blinding

A double-blinding technique with in-house blinding will be used. Ceftolozane/tazobactam plus metronidazole and meropenem plus placebo will be packaged identically so that blinding is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

An unblinded pharmacist will prepare IV study treatment. In addition, infusion bags, IV lines, and any other dispensing devices will be covered as needed to maintain blinding.

The standard of care oral step-down therapy used at the discretion of the investigator after completion of IV study treatment will not be blinded.

Specific blinding procedures required for this study can be found in the pharmacy manual.

See Section 7.1.4.4, Subject Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization

Treatment randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 3:1 ratio to ceftolozane/tazobactam plus metronidazole or meropenem plus placebo, respectively.

5.4 Stratification

Treatment randomization will be stratified across 5 age groups as defined in Section 2.1 – Trial Design. After the minimum enrollment targets in Section 2.1 for each age group are met (202 subjects total), additional subjects (combined across MK-7625A-034 and MK-7625A-035) will be enrolled in any of the 5 age groups.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

The following concomitant medications/therapies are not permitted in this study:

- Immunosuppressive agents

  NOTE: 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.

- Valproic acid or divalproex sodium
- Probenecid
- Disulfiram
- Ergot derivatives
- Ethanol-containing medications
- Nonstudy systemic (IV or oral) antibacterial treatments

  NOTE: Subjects who require empiric enterococcal coverage for the index cIAI may receive concomitant therapy with an enterococcal antibiotic with activity limited to gram-positive coverage (eg, vancomycin, daptomycin, teicoplanin, linezolid). One dose of prophylactic antibiotic with gram-negative activity is allowed.

  Subjects who require empiric antifungal coverage for the index cIAI may receive concomitant antifungal coverage with an azole, echinocandin or polyene antifungal as chosen by the investigator based on local standard of care.

The following medications are permitted, although their efficacy and safety should be clinically monitored and/or serum levels followed with appropriate dosage adjustments as necessary at the initiation of study drug, periodically during treatment, and after discontinuation of study drug:

- Lithium
- Phenytoin
- Warfarin
- Carbamazepine
- Medications resulting in prolonged QT interval

All other concomitant medications necessary for the health and well-being of the subject are permitted.

5.6 Rescue Medications & Supportive Care

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

5.7 Diet/Activity/Other Considerations

Intravenous study treatment may be administered without regard to food or caffeine consumption, tobacco use, or activity. Subjects should not consume alcohol while on IV study treatment due to potential interaction with metronidazole.

Oral step-down study therapy may have different dietary considerations from IV study treatment and should be administered according to the product label.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of IV study treatment or oral step-down therapy does not represent withdrawal from the trial.

As certain data on clinical events beyond study treatment discontinuation are important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued study treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.9 – Subjects Who Prematurely Discontinue from Study Treatment or the Trial.

Subjects may discontinue study treatment at any time for any reason or be dropped from study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from IV study treatment or oral step-down therapy but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue study treatment.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk from continued administration of study treatment.
- Development of moderate or severe impairment of renal function, including an estimated CrCL <50 mL/min/1.73 m^2 based on the revised Schwartz equation [12] or requirement for peritoneal dialysis, hemodialysis, or hemofiltration (required for IV study treatment only).

- The investigator feels it is in the best interest of the subject to discontinue for any reason, including, but not limited to, the need for nonstudy antibacterial therapy due to insufficient therapeutic effect of the study treatment.

- Safety issues:

  - Occurrence of an AE or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from IV study treatment or oral step-down therapy. In the event that IV study treatment or oral step-down therapy is discontinued due to the occurrence of an AE, the trial site should notify the Sponsor as soon as possible.

  - Suspected or confirmed pregnancy or breastfeeding during the IV study treatment or oral step-down therapy administration period. Female subjects whose pregnancy test becomes positive during study treatment must be followed through the immediate postnatal period or until termination of the pregnancy.

Discontinuation from study treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart study treatment.

5.8.2 Withdrawal from the Trial

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from study treatment or withdraws from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject (or their legally acceptable representative) provides documented informed consent. The overall trial ends when the last data are available in either MK-7625A-034 or MK-7625A-035 (whichever is later).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial 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 trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial 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.

6.0 TRIAL FLOW CHART

Trial Period:	Screening	Treatment (5 to 14 days)[a]					Follow-up	
Visit Number:	1	2	3 to 16	17	18	19	20	21
Visit Title:	Screening[b]	Randomization[b]	IV Clinical Assessments[a,b]	EOIV[c] (all subjects)	Oral Clinical Assessment[d,e] (only for IV to oral switch)	EOT[d] (only for IV to oral switch)	TOC (all subjects)	LFU[f] (all subjects)
Scheduled Day or Timing:	48 h	Day 1	Day 2 up to Day 15	<24 h after last IV dose	(after ≥7 days on oral step-down therapy)	<48 h after last oral dose	7 to 14 days after final dose	21 to 28 days after final dose
Administrative Procedures								
Informed consent	X							
Inclusion/exclusion criteria	X							
Subject identification card	X	X						
Medical history	X							
Prior or concomitant medication review	X	X	X	X	X	X	X	X
Randomize to treatment (prior to administration of study treatment)		X						
Administer IV ceftolozane/tazobactam + metronidazole or IV meropenem + placebo every 8 h		X	X					
Standard of care oral step-down therapy[a]					X			
Clinical Procedures/Assessments								
Body weight	X	X[g,h]	X[g,h]	X[g]	X[g,h]	X[g]		
Height	X							
Vital signs (heart rate, respiratory rate, blood pressure, and temperature)	X	X	X	X	X	X	X	X[g,i]
Full physical examination	X							
Directed physical examination			X[j]	X	X	X	X	X[g,i]
Record surgical wound examination[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g,i]
Abdominal sign/symptom assessment	X	X	X	X	X	X	X	X[g,i]
Record summary of operative procedures (as indicated/done)	X	X	X	X	X	X	X	

Trial Period:	Screening	Treatment (5 to 14 days)[a]					Follow-up	
Visit Number:	1	2	3 to 16	17	18	19	20	21
Visit Title:	Screening[b]	Randomization[b]	IV Clinical Assessments[a,b]	EOIV[c] (all subjects)	Oral Clinical Assessment[d,e] (only for IV to oral switch)	EOT[d] (only for IV to oral switch)	TOC (all subjects)	LFU[f] (all subjects)
Scheduled Day or Timing:	48 h	Day 1	Day 2 up to Day 15	<24 h after last IV dose	(after ≥7 days on oral step-down therapy)	<48 h after last oral dose	7 to 14 days after final dose	21 to 28 days after final dose
Record radiological examination	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
AE monitoring[k]		X	X	X	X	X	X	X
Assess clinical outcome				X		X	X	
Laboratory Procedures/Assessments								
Blood for hematology and chemistry safety evaluations	X		X[j]	X[l]	X	X[l]	X	X[g,i]
Coombs test (direct)	X			X				
Serum pregnancy test[m]	X[m]						X[m]	
Assessment of CrCL	X		X[g]	X[g]	X[g]	X[g]		
Intra-abdominal sample for culture and susceptibility testing	X[n]		X[g]	X[g]	X[g]	X[g]	X[g]	
Blood for culture and susceptibility testing[g]	X[g]		X[g]	X[g]				
Blood for PK analyses (Day 3 only [after ≥6 doses of IV study treatment])[o]			X[o]					

AE = adverse event; CrCL = creatinine clearance; eCRF = electronic case report form; EOIV = End of IV Treatment; EOT = End of Treatment; h = hour(s); IV = intravenous; LFU = Last Follow-up; PK = pharmacokinetic(s); SAE = serious adverse event; TOC = Test of Cure

[a] After receiving at least 9 doses of double-blind IV study treatment, subjects in either treatment arm may be switched to open-label, standard of care oral step-down antibiotic therapy at the investigator's discretion. Total duration of study treatment (IV only or IV + oral) is a minimum of 5 days and a maximum of 14 days, except the final day of study treatment may extend into Day 15 to accommodate different start and stop times of the IV study treatment and/or dosing schedules of the oral step-down therapy From Day 1 through the last day of IV study treatment, each subject's assessments should be performed at a consistent time of day (eg, every morning) on each calendar day, as much as possible. Subjects cannot go home on IV study treatment. If subjects are switched to oral step-down therapy, the oral step-down therapy must be initiated within <24 hours after stopping IV study treatment.

[b] Screening, randomization, and first dose of study treatment may all occur on the same day. Assessments (eg, laboratory procedures, vital signs) performed prior to providing documented informed consent may be used if collected during the routine care of the patient, so long as they were conducted within 48 hours prior to the start of administration of the first dose of IV study treatment.

[c] For subjects who receive only IV study treatment and are not switched to oral step-down therapy, the EOIV Visit serves as the EOT Visit and these subjects do not have a separate EOT Visit. Subjects who are switched to oral step-down therapy will have both an EOIV and an EOT Visit.

[d] Only for subjects who are switched to oral step-down therapy.

[e] An Oral Clinical Assessment Visit should be performed once if a subject receives ≥7 days of oral step-down therapy. This visit can be performed ±24 hours after 7 days of oral step-down therapy. Subjects who receive <7 days of oral step-down therapy will not undergo the Oral Clinical Assessment Visit. Any AE that comes to the attention of the investigator before the Oral Clinical Assessment Visit should be recorded at this visit, but any SAE must be reported within 24 hours. The Oral Clinical Assessment Visit will be the same whether the subject is still in the hospital or has been discharged to home.

[f] The LFU Visit will be conducted by telephone; however, if the subject has abnormal laboratory values or AEs that require follow-up, an in-person visit is required.

[g] If clinically indicated.

[h] As needed to calculate CrCL or changes in weight-based dosing, if the subject's weight is expected to change over the course of IV study treatment.

[i] To be performed only if LFU Visit is conducted in person instead of by telephone.

[j] Procedures to be completed on Day 3 and then once weekly while the subject is receiving study treatment (IV or oral).

[k] The reporting period for AEs outlined in Section 7.2. All serious adverse events will be followed until resolution, stabilization, withdrawal of consent, or death.

[l] If blood samples for chemistry and hematology safety evaluations were collected within 24 hours prior to the EOIV or EOT Visit, blood samples for these evaluations are not required at the visit.

[m] Female subjects of childbearing potential only. A urine pregnancy test instead of a serum pregnancy test may be performed at the TOC Visit, if deemed clinically appropriate by the investigator.

[n] Baseline intra-abdominal specimen collection in compliance with Section 7.1.3.4 – Intra-abdominal Samples for Culture. Subjects who are enrolled preprocedure should have a sample obtained during the interventional procedure performed to comply with Section 7.1.3.4.

[o] Blood samples for ceftolozane, tazobactam, and tazobactam M1 concentration assays will be collected from all subjects over one 8-h dosing period on Day 3 of the treatment period after administration of at least 6 doses of IV study treatment (see Section 7.1.3.6 – Pharmacokinetic Evaluations). On Day 3, 250 µL of blood will be collected at the following times: At the end of infusion (collected within 10 minutes after the end of total dose administration); between 2.5 and 3.5 hours post start of infusion; and between 5.0 and 6.0 hours post start of infusion but prior to the start of the next dose of study treatment. If sampling on Day 3 is logistically difficult, sampling may be performed at comparable time points after Day 3 in subjects who are continuing to receive IV study treatment. Plasma will be separated from blood and sent to the central laboratory for PK testing. Procedures for collection, processing, storage, and shipment of PK samples from blood (plasma) will be provided separately in a laboratory manual. Actual whole blood sample collection dates and times should be recorded on the appropriate eCRF.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent, and assent if applicable, from each potential subject or each subject's legally acceptable representative prior to participating in this clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented consent/assent is in place.

7.1.1.1.1 General Informed Consent/Assent

Informed consent/assent given by the subject or their legally acceptable representative must be documented on a consent/assent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the subject (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent/assent form should be given to the subject (or their legally acceptable representative) before participation in the trial.

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

Specifics about a trial and the trial population are to be included in the trial informed consent/assent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements. The assent, as applicable, will adhere to IRB/ERC requirements, applicable laws and regulations, and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides documented informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. In addition to the evaluation of a subject's medical history in terms of study eligibility, all medical conditions present during the 5 years prior to study entry will be documented at the Screening Visit on the appropriate eCRF. Any history of prior cIAI episodes or conditions that may predispose a subject to the development of cIAI will also be documented on the appropriate eCRF, even if the prior episode or predisposing condition was diagnosed more than 5 years prior to study entry.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

At Screening, the investigator or qualified designee will review prior medication use and record prior medication taken by the subject within 7 days before the first dose of trial medication (or within 14 days before the first dose of trial medication for all antibacterial agents, and within 30 days before the first dose of trial medication for any other investigational drug). For subjects who are breastfeeding, prior medication use by the subject's mother will be recorded similarly.

Any blood or blood product transfusions in the previous 48 hours before first dose of trial medication will be recorded.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial (from the first dose of trial medication to the last trial evaluation). For subjects who are breastfeeding, concomitant medication use by the subject's mother will be recorded similarly.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Specific details on the Screening Visit requirements are provided in Section 7.1.5.1 - Screening.

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

7.1.1.8 Trial Compliance (Medication)

Interruptions from the protocol specified IV study treatment for ≥2 consecutive doses or ≥3 nonconsecutive doses require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.2 Clinical Procedures/Assessments

Clinical procedures and assessments will occur as specified in Section 6.0 – Trial Flow Chart. This section provides additional details. Clinical procedure/assessment data will be recorded in source documents and the appropriate location in the eCRF.

7.1.2.1 Body Weight, Height, and Vital Signs

The investigator or qualified designee will record body weight (kg) and height (cm) as indicated in Section 6.0 – Trial Flow Chart. Body weight will be measured without shoes, jacket, or diaper (in subjects using diapers).

The investigator or qualified designee will record vital signs (heart rate, respiratory rate, blood pressure, and temperature [oral, tympanic, rectal, axillary, or temporal]) as indicated in Section 6.0 – Trial Flow Chart. Systolic and diastolic blood pressure will be measured on the same arm. Heart rate and blood pressure will be measured simultaneously.

7.1.2.2 Physical Examination

The investigator or qualified designee will perform full or directed physical examinations as indicated in Section 6.0 – Trial Flow Chart. The investigator or qualified designee will also perform a full or directed physical examination at other times at the investigator's discretion, if an AE or abnormality is suspected.

The full physical examination will include examination of body systems (including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system).

The directed physical examination should be based on the subject's condition and circumstances, at the investigator's discretion. The directed physical examination should note any changes in the subject's condition (body systems) since the last examination and does not preclude examination of any of the body systems as clinically indicated.

Changes in physical examination findings (abnormalities) that the investigator considers clinically significant will be recorded on the medical history eCRF page if observed prior to administration of the first dose of IV study treatment. Changes in physical examination findings (abnormalities) that the investigator considers clinically significant must be recorded as AEs if observed after the start of the first dose of IV study treatment.

7.1.2.3 Surgical Wound Examination

Surgical wound examination is performed as clinically indicated and noted in Section 6.0 – Trial Flow Chart to assess signs of infection such as skin erythema, induration, tenderness, warmth, fluctuance, swelling, and wound pain. If signs of infection are present, findings will be recorded and categorized as present, absent, or unable to assess. If wound discharge is present, the nature of the discharge (nonpurulent or purulent) will be assessed. This assessment should ideally be performed at the same time each day.

7.1.2.4 Abdominal Sign and Symptom Assessment

The abdominal signs and symptoms of cIAI (see Section 5.1.2 - Subject Inclusion Criteria, Criterion 4) will be evaluated and graded as absent, present, or unable to assess at the visits specified in Section 6.0 – Trial Flow Chart. The signs and symptoms of cIAI (eg, fever, leukocytosis, hypotension, abdominal pain, nausea/vomiting, anorexia, abdominal mass on clinical examination, and altered mental status) will be assessed at Screening by clinical examination of the abdomen and noted as absent, present, or not able to assess/not performed.

At visits after Screening, the investigator will assess each observed sign or symptom according to the categories above. The clinical signs and symptoms of cIAI are not considered AEs, unless a sign or symptom qualifies as an SAE.

7.1.2.5 Summary of Operative Procedures

A summary of interventional operative procedures to treat cIAI will be recorded. The anatomic site of infection, the presence of one or more abscesses, the extent of peritonitis, and the etiological mechanism (eg, trauma, postoperative, or spontaneous rupture) must be recorded. Copies of all surgical reports must be retained for review during monitoring visits.

7.1.2.6 Radiological Examination

Specific radiographic examinations are not required for this study unless the subject is enrolled preoperatively. Radiological examinations should only be performed as required for routine clinical management. Radiological evaluations might include plain abdominal radiograph, computed tomography (CT) scan, ultrasound, and/or magnetic resonance imaging (MRI) scan, with or without contrast. The results of any such studies should be recorded. Copies of all interventional radiological reports and diagnostic study reports must be retained for review during monitoring visits.

7.1.2.7 Adverse Event Monitoring

Assessment and recording of AEs is described in Section 7.2 – Assessing and Recording Adverse Events. All SAEs will be followed until resolution, stabilization, withdrawal of consent, or death.

7.1.2.8 Assessment of Clinical Outcome

At the visits indicated in Section 6.0 – Trial Flow Chart, the investigator or qualified designee will assign the subject's clinical outcome to a category (cure, partial improvement, failure, or indeterminate) as described in Section 4.2.3.2 – Rationale for Efficacy Endpoints.

7.1.2.9 Assessment of Microbiological Outcome

All microbiological outcomes will be assessed by the Sponsor based on culture results, as defined in Section 4.2.3.2 – Rationale for Efficacy Endpoints. Investigators are not responsible for assessment of microbiological outcomes.

7.1.2.10 Assessment of Emergent Infection

Emergent pathogens (ie, those isolated after Screening) will be assessed by the Sponsor for the outcome of superinfection or new infection, as defined in Section 4.2.3.2 – Rationale for Efficacy Endpoints. Investigators are not responsible for assessment of emergent infections.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory procedure/assessment data will be recorded in source documents and the appropriate location in the eCRF.

The total amount of blood to be drawn/collected over the course of the trial (from screening to the last trial evaluation), including approximate blood volumes drawn/collected by visit per subject, can be found in Appendix 12.2.

7.1.3.1 Laboratory Safety Evaluations (Hematology and Chemistry)

At the visits specified in Section 6.0 – Trial Flow Chart, blood samples will be obtained for the indicated laboratory tests (hematology and chemistry; Table 8). See Appendix 12.2 – Approximate Blood Volumes Drawn/Collected by Trial Visit for the maximum expected blood volumes needed for laboratory tests.

At Screening, blood samples will be collected for laboratory safety evaluations to determine trial eligibility, as follows: serum creatinine, ANC, AST, ALT, and total bilirubin. These laboratory safety evaluations for trial eligibility will be performed by the local laboratory. A blood sample will also be collected at Screening for the direct Coombs test, which the site will send to the central laboratory for testing.

Blood samples collected for laboratory safety evaluations after the Screening Visit will be tested by the local laboratory. At the EOIV Visit, a blood sample will be collected for the direct Coombs test, which the site will send to the central laboratory for testing. The blood sample for direct Coombs test may be drawn on Day 3 (with the blood samples for chemistry and hematology safety evaluations) if the EOIV Visit is planned for Day 4.

Blood samples for laboratory safety evaluations will be collected without regard to meals or study treatment.

Table 8 Laboratory Safety Evaluations

Hematology	Chemistry
Hematocrit Hemoglobin Platelets Leukocytes (total and differential) Direct Coombs test	Albumin Alkaline phosphatase ALT AST Bicarbonate Calcium Chloride Creatinine Glucose Phosphorus Potassium Sodium Total bilirubin Direct bilirubin, if total bilirubin is >ULN
	Total protein BUN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal
NOTE: All laboratory safety evaluations will be performed by the local laboratory, except the direct Coombs test; sites will send blood samples for the direct Coombs test to the central laboratory for testing.

7.1.3.2 Pregnancy Testing

Pregnancy testing will be performed by the local laboratory on female subjects of child-bearing potential at the visits specified in Section 6.0 – Trial Flow Chart. Prior to randomization, the investigator will ensure serum pregnancy tests are negative in female subjects of child-bearing potential.

A urine pregnancy test instead of a serum pregnancy test may be performed at the TOC Visit by the local laboratory, if deemed clinically appropriate by the investigator.

7.1.3.3 Assessment of Creatinine Clearance

Blood samples for serum creatinine will be obtained as indicated in Section 6.0 – Trial Flow Chart and evaluated by the local laboratory. The subject's CrCL will be estimated using the serum creatinine value, height, and the revised Schwartz equation [12], as follows:

Glomerular filtration rate (GFR) (mL/min per 1.73 m^2) = 0.413 * H/S_{cr}, where

- GFR = glomerular filtration rate (mL/min per 1.73 m^2)
- H = height (cm)
- S_{cr} = serum creatinine (mg/dL)

For subjects with unstable renal function (CrCL is close to 50 mL/min/1.73 m^2) while receiving IV study treatment, obtain serum creatinine value and monitor CrCL at least daily. Subjects with CrCL <50 mL/min/1.73 m^2 must be discontinued from the IV study treatment.

7.1.3.4 Intra-abdominal Samples for Culture

The investigator or qualified designee will obtain intra-abdominal specimens at the visits specified in Section 6.0 – Trial Flow Chart for culture of aerobic and anaerobic organisms during the interventional 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, and swabs of purulent material are discouraged. Specimens should not be obtained from in situ abdominal drains.

Thereafter, specimens for culture are to be obtained from the site of infection, if clinically indicated (eg, if re-intervention is required, collection during the additional surgery in subjects with clinical failure) to evaluate the microbiological assessment. Specimens should not be obtained from in situ abdominal drains. Culture of the intra-abdominal specimen, isolation of pathogen(s), initial identification of pathogen(s), and susceptibility testing will be conducted by the local laboratory. The result of culture and initial identification of pathogen(s) at the local laboratory should be recorded in the source document and eCRF. The sites should ship the isolated pathogen(s) to the central microbiology laboratory for re-identification and MIC testing. Further details of the procedures to be followed for sample collection, storage, and shipment will be provided in a laboratory manual.

7.1.3.5 Blood Samples for Culture

Blood samples are collected for culture as specified in Section 6.0 – Trial Flow Chart. Blood samples for culture should be collected if signs of sepsis appear at any time during the study. Further details of the procedures to be followed for sample collection, storage, and shipment will be provided in a laboratory manual.

Blood samples for culture will be obtained for all subjects at Screening if clinically indicated. Culture of the blood specimen, isolation of pathogen(s), initial identification of pathogen(s), and susceptibility testing will be conducted by the local laboratory and recorded. The sites will ship the isolated pathogen(s) to the central microbiology laboratory for re-identification and MIC testing. Further details of the procedures to be followed for sample collection, storage, and shipment will be provided in a laboratory manual.

7.1.3.6 Pharmacokinetic Evaluations

Whole blood to obtain plasma samples will be collected for population PK analysis of ceftolozane and tazobactam as specified in Section 6.0 – Trial Flow Chart. These samples may also be used in the assessment of the clinical relationship between ceftolozane and tazobactam plasma concentrations and efficacy, as appropriate.

Blood samples for ceftolozane, tazobactam, and tazobactam M1 concentration assays and plasma PK parameters (for ceftolozane and tazobactam) will be collected from all subjects over one 8-hour dosing period on Day 3 of the treatment period after administration of at least 6 doses of IV study treatment. These blood samples will be collected at the following times: At the end of infusion (collected within 10 minutes after the end of total dose administration); between 2.5 and 3.5 h post start of infusion; and between 5.0 and 6.0 hours post start of infusion but prior to the start of the next dose of study treatment.

Pharmacokinetic sample collection may occur on Day 4 if the last dosing period of Day 3 is selected for PK sample collection. Additionally, if sampling on Day 3 is logistically difficult, sampling may be performed at comparable time points after Day 3 in subjects who are continuing to receive IV study treatment.

Plasma will be separated from blood and sent to the central laboratory for PK testing. Details of the procedures for collection, processing, storage, and shipment of PK samples from blood (plasma) will be provided separately in a laboratory manual. Actual whole blood sample collection dates and times must be recorded.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue study treatment prior to completion of the study treatment regimen (IV only or IV + oral) should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the EOIV or EOT Visit, as described in Section 7.1.5.9 –Subjects Who Prematurely Discontinue From Study Treatment or the Trial, should be performed at the time of discontinuation. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.2 Lost to Follow-up

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

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject 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 subject at each missed visit (eg, phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

NOTE: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.3 Unblinded Pharmacist

Subjects will receive the IV study treatment, following preparation by an unblinded pharmacist (Section 5.2.6 – Trial Blinding), for a maximum of 14 days. Preparation of study drug by the unblinded pharmacist is detailed in the pharmacy manual. Importantly, the unblinded pharmacist will be uninvolved in any of the postinfusion evaluations for the subject. All study personnel involved with the postinfusion evaluations of safety and efficacy outcomes, including the study coordinator(s), investigator, or subinvestigator(s), must have no access to the treatment group assignment or the preparation of the study infusion.

7.1.4.4 Subject Blinding/Unblinding

When the investigator or delegate needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse events, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate 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 subject's treatment assignment, the investigator or delegate must enter the intensity grade of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or nonstudy treating physician should continue to be monitored in the trial.

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 trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

Treatment/Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., 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.

Subjects whose treatment assignment has been unblinded should continue to receive study medication.

7.1.4.5 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Refrigerators or freezers used to store study medication or subject samples/specimens that will be sent to the central laboratory.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Screening assessments are performed within 48 hours prior to the start of administration of the first dose of IV study treatment. Assessments (eg, laboratory procedures, vital signs) performed prior to providing documented informed consent may be used if collected during the routine care of the subject, so long as they were conducted within 48 hours prior to the start of administration of the first dose of IV study treatment. Potential subjects are evaluated at the Screening Visit to determine if they fulfill the entry requirements in Section 5.1 –

Entry Criteria. All Screening results must be available prior to randomization. Screening, randomization, and first dose of study treatment may all occur on the same day.

7.1.5.2 Randomization Visit

The Randomization Visit is the date subjects are randomized to treatment arms, and may then receive the first dose of double-blind IV study treatment. Screening, randomization, and first dose of study treatment may all occur on the same day.

7.1.5.3 Clinical Assessment Visits on Intravenous Study Treatment

Clinical Assessment Visits on IV study treatment occur daily on Day 2 through the last dose of IV study treatment. At these visits, each subject's assessment should be performed at a consistent time each day (eg, every morning), as much as possible. Safety laboratory tests and a directed physical examination should be completed on Day 3 (±24 hours) and then once weekly while the subject is receiving IV study treatment. Subjects cannot go home on IV study treatment.

Blood is collected for PK analyses on Day 3 (after ≥6 doses of IV study treatment). Pharmacokinetic sample collection may occur on Day 4 if the last dosing period of Day 3 is selected for PK sample collection. Additionally, if sampling on Day 3 is logistically difficult, sampling may be performed at comparable time points after Day 3 in subjects who are continuing to receive IV study treatment.

7.1.5.4 End of IV Treatment Visit

The EOIV Visit occurs in all subjects within 24 hours after the last dose of IV study treatment. For subjects who receive only IV study treatment and are not switched to oral step-down therapy, the EOIV Visit serves as the EOT Visit and these subjects do not have a separate EOT Visit. Subjects who are switched to oral step-down therapy will have both an EOIV and EOT Visit. If subjects are switched to oral step-down therapy, the oral step-down therapy must be initiated <24 hours after stopping IV study treatment. If blood samples for chemistry and hematology safety evaluations were collected within 24 hours prior to the EOIV Visit, blood samples for these evaluations are not required at this visit.

7.1.5.5 Clinical Assessment Visit on Oral Step-down Therapy

The Oral Clinical Assessment Visit is completed only for subjects who are switched to oral step-down therapy. If subjects are switched to oral step-down therapy, the oral step-down therapy must be initiated <24 hours after stopping IV study treatment. This visit should be performed once if the subject receives ≥7 days of oral step-down therapy. This visit can be performed ±24 hours after 7 days on oral step-down therapy. Subjects who receive <7 days of oral step-down therapy will not undergo this visit. Any AE that comes to the attention of the investigator before the Oral Clinical Assessment Visit should be recorded at this visit, but any SAE must be reported within 24 hours. This visit will be the same whether the subject is still in the hospital or has been discharged to home. If the Oral Clinical Assessment Visit and EOT Visit are on the same day, only the EOT Visit should be completed.

7.1.5.6 End of Treatment Visit

The EOT Visit occurs only in subjects who are switched to oral step-down therapy. These subjects will have both an EOIV and EOT Visit. This visit will occur within 48 hours after the last dose of oral step-down therapy. If blood samples for chemistry and hematology safety evaluations were collected within 24 hours prior to the EOT Visit, blood samples for these evaluations are not required at this visit.

7.1.5.7 Test of Cure Visit

The TOC Visit occurs in all subjects 7 to 14 days after the final dose of study treatment (IV or oral).

7.1.5.8 Last Follow-up Visit

The LFU Visit occurs in all subjects 21 to 28 days after the final dose of study treatment (IV or oral). The LFU Visit will be conducted by telephone; however, if the subject has abnormal laboratory values or AEs that require follow-up, an in-person visit is required.

7.1.5.9 Subjects Who Prematurely Discontinue From Study Treatment or the Trial

Subjects who discontinue from study treatment prior to completion of the study treatment regimen (IV only or IV + oral) will continue to be monitored in the trial according to Section 6.0 – Trial Flow Chart.

For subjects who prematurely withdraw from the trial, see Section 7.1.4.1 – Withdrawal/Discontinuation and Section 7.1.4.2 – Lost to Follow-up.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo

or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the subject provides documented informed consent but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through the last trial evaluation (Last Follow-up visit, 21 to 28 days after final dose), all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose greater than 1.5 times higher than the weight-based dosing specified for the subject's age group for ceftolozane/tazobactam, meropenem, and metronidazole. For oral step-down antibiotic therapy, refer to the manufacturer's label for overdose criteria. Additional details are described in the pharmacy manual.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject

(spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the documented informed consent form is provided but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported. 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.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 9 for additional details regarding each of the above criteria.

For the time period beginning when the subject provides documented informed consent until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through the last trial evaluation (Last Follow-up visit, 21 to 28 days after final dose), any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. For the time period from the signing of informed consent through treatment allocation/randomization, only serious adverse events that either cause the participant to be excluded from the trial or are the result of a protocol-specified intervention, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent). All serious adverse events will be followed until resolution, stabilization, withdrawal of consent, or death.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the subject provides documented informed consent until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through the last trial evaluation (Last Follow-up visit, 21 to 28 days after final dose), any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. 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 trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. An overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 9. The investigator's assessment of causality is required for each adverse event. Refer to Table 9 for instructions in evaluating adverse events.

Table 9 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient 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 a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event 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 drug and the adverse event 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 adverse event:	
	Exposure	Is there evidence that the subject 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 trials 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

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	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 trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH 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 SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment 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.		
Record one of the following:	**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	Subject 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 subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Executive Oversight Committee

The EOC comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the trial.

7.3.2 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external DMC will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the trial. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the trial. For any analyses in the sSAP and protocol, the sSAP will supersede those described in the protocol. Post hoc exploratory analyses will be detailed in the CSR.

Key elements of the Statistical Analysis Plan are summarized in Section 8.1. The comprehensive plan is provided in Sections 8.2 through 8.12.

8.1 Statistical Analysis Plan Summary

Trial Design Overview	A Phase 2, randomized, active comparator-controlled, multicenter, double-blind, clinical trial to study the safety and efficacy of ceftolozane/tazobactam (MK-7625A) plus metronidazole versus meropenem in pediatric subjects with complicated intra-abdominal infections.
Treatment Assignment	Approximately 240 pediatric subjects (combined across MK-7625A-034 and MK-7625A-035) in 5 age groups will be enrolled and randomized in a 3:1 ratio to receive IV ceftolozane/tazobactam plus metronidazole or IV meropenem plus placebo, respectively. The total duration of study treatment will be a minimum of 5 days to a maximum of 14 days. Randomization will be stratified by age group. See Table 6 for target enrollments and IV dosage regimens for each age group.
Analysis Populations	Safety: All Subjects as Treated (ASaT) Population Pharmacokinetics: PK Population Efficacy: Modified Intent-to-Treat (MITT), Microbiological Modified Intent-to-Treat (mMITT), Microbiologically Evaluable (ME), and Clinically Evaluable (CE) Populations
Primary Endpoints	The primary safety parameters will include the following safety evaluations: • AEs • Clinical laboratory tests • Vital signs
Key Secondary Endpoints	• Clinical success at the EOT and TOC Visits • Per-subject microbiological eradication at the EOT and TOC Visits
Statistical Methods for Key Efficacy/PK Analyses	A 2-sided 95% confidence interval (CI) based on the M&N method [20] stratified by age group will be provided to evaluate the treatment differences for clinical success at the EOT and TOC Visits and per-subject microbiological eradication at the EOT and TOC Visits. There will be no efficacy hypothesis testing in this estimation trial.
Statistical Methods for Key Safety Analyses	Tier 2 endpoints include AEs of elevated laboratory values; the percentage of subjects with any AE, any SAE, and any treatment-related AE; any serious and study treatment-related AE; the percentage of subjects who discontinue due to an AE; and AEs (specific preferred terms), system organ classes, or values outside of the local laboratory's reference range with frequency ≥6 subjects in the experimental treatment arm and/or ≥2 subjects in the comparator treatment arm. The 95% CIs will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the unstratified M&N method [20], an unconditional, asymptotic method. Changes in laboratory and vital sign values from baseline will be summarized as Tier 3 events using descriptive statistics.
Interim Analyses	No interim analyses for efficacy are planned for this trial. However, an external DMC will convene to review combined safety data from the present trial and the companion Phase 2 trial in pediatric subjects with cUTI (MK-7625A-034). Additional details are available in the external DMC charter.
Multiplicity	There will be no adjustment for multiplicity in this estimation trial.

Sample Size and Power	Approximately 240 subjects (combined across MK-7625A-034 and MK-7625A-035) will be enrolled with approximately 180 subjects in the ceftolozane/tazobactam plus metronidazole arm and approximately 60 subjects in the meropenem plus placebo arm. The estimated differences and 95% CIs for event rate under various scenarios for the combined trials are presented in Table 14 . For example, if the overall event rate is 10% across both treatment arms (18 out of 180 and 6 out of 60 subjects, respectively), the 95% CI for the between-treatment difference is -13.4, 8.5.

8.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this trial will be the responsibility of the Sponsor's Clinical Biostatistics department.

This trial will be conducted as a double-blind trial under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations 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 via an IVRS/IWRS.

The interim review of the safety data will be performed by the external DMC (Section 7.3.2 – Data Monitoring Committee). Treatment level results will be provided by the external unblinded statistician to the external DMC. Limited additional Sponsor personnel may be unblinded to the treatment level results of the safety analyses, if required, in order to act on the recommendations of the external DMC. The extent to which individuals are unblinded with respect to results of safety review will be documented by the unblinded statistician.

The external DMC will serve as the primary reviewer of the safety results from this study with respect to the safety reviews and will make recommendations for discontinuation of or modifications to the study to the EOC of the Sponsor (Section 7.3.1 – Executive Oversight Committee). If the external DMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC (internal to the Sponsor) may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistic details will be provided in the external DMC charter.

Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the interim safety review(s).

Pharmacokinetic data will be unblinded early for the purpose of preparing a population PK model. A separate Modeling and Simulation Plan authored by the department of Quantitative Pharmacology and Pharmacometrics will describe the modeling work to be performed. A small team, who are separate from the protocol team, will be unblinded for the purpose of preparing the population PK model. Efficacy and safety data will not be unblinded. Interim data or results will not be shared with the protocol team before study unblinding.

8.3 Hypotheses/Estimation

Objectives of the trial are stated in Section 3.0 – Objective(s) & Hypothesis(es). No efficacy or safety hypothesis testing will be conducted in this estimation trial.

8.4 Analysis Endpoints

Safety and efficacy endpoints that will be evaluated for between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Safety Endpoints

In order to evaluate the safety and tolerability of ceftolozane/tazobactam, the following safety endpoints will be summarized based on the ASaT population: AEs, laboratory data, and vital signs.

An initial description of safety measures is provided in Section 4.2.3.1 – Rationale for Safety Endpoints and Events of Clinical Interest (ECIs) are defined in Section 7.2.3.2 – ECIs. The proportion of subjects who experience AEs of elevated laboratory values that are reported as ECIs during the study treatment period will be estimated.

8.4.1.1 Adverse Events

The proportion of subjects with AEs of the following types at any time from the first dose of study treatment to the last trial evaluation will be investigated: (1) Any AE, (2) any SAE, (3) any drug-related AE, (4) any serious and drug-related AE, and (5) any AE leading to study treatment discontinuation.

8.4.1.2 Laboratory Data

For the summaries of laboratory tests, subjects must have both a baseline and postrandomization on-treatment measurement to be included. Subjects' laboratory values (based on their most abnormal laboratory test values, in the direction of interest, while on study treatment) will be classified as to whether or not they fall outside of the local laboratory's reference range and are worse in grade (ie, more abnormal in the direction of interest) than at baseline.

Summaries of laboratory changes from baseline to the EOIV, EOT, and TOC Visits, and from baseline to the LFU Visit, as data permit, will be presented.

The number and percentage of subjects in each treatment arm with an elevated AST or ALT level (>3 × ULN, >5 × ULN, and >10 × ULN) and bilirubin level (>1.5 × ULN and >2 × ULN) will be presented by trial visit (as specified in Section 6.0 - Trial Flow Chart) for the ASaT population.

A listing of subjects who meet the following predetermined laboratory criteria will also be provided for the ASaT population, including 1) ALT or AST >3 × ULN, alkaline

phosphatase ≤2 × ULN, and total bilirubin >1.5 × ULN and 2) ALT or AST >3 × ULN, alkaline phosphatase ≤2 × ULN, and total bilirubin >2 × ULN.

8.4.1.3 Vital Signs

Vital sign parameters will include heart rate (beats per minute), respiratory rate (breaths per minute), systolic and diastolic BP in mm mercury (Hg), and temperature in degrees Celsius (°C) by treatment group and trial day/visit.

Other safety parameters include physical examinations and standard laboratory safety tests at time points specified in Section 6.0 - Trial Flow Chart.

8.4.2 Efficacy Endpoints

There are no primary efficacy endpoints for this study; the primary endpoints are safety parameters (Section 8.4.1 – Safety Endpoints).

8.4.2.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Clinical success rate at the EOT and TOC Visits, defined as the proportion of subjects in the analysis population who have a clinical response of cure.
- Per-subject microbiological success rate at the EOT and TOC Visits, defined as the proportion of subjects in the analysis population who have microbiological eradication or presumed eradication of all baseline pathogens.

NOTE: For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate assessment does not need to be performed at the EOT Visit; the EOIV Visit will serve as the EOT Visit.

Clinical outcome categories are defined in Table 3 and microbiological outcome categories are defined in Table 4 in Section 4.2.3.2 – Rationale for Efficacy Endpoints.

8.4.2.2 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Clinical success rate at the EOIV Visit, defined as the proportion of subjects in the analysis population who have a clinical response of cure or partial improvement.

  NOTE: At EOIV, clinical success is defined as cure or partial improvement. At EOT and TOC, clinical success is defined as cure. The definition for clinical success at the EOIV Visit includes partial improvement to accommodate those subjects with partial improvement who are switched to oral step-down therapy at this time point.

- Per-subject microbiological success rate at the EOIV Visit, defined as the proportion of subjects in the analysis population who have a microbiological outcome of eradication or presumed eradication of all baseline pathogens.

- Per-pathogen microbiological success rate at the EOIV, EOT, and TOC Visits, defined as the proportion of baseline pathogens that have an outcome of microbiological eradication or presumed eradication.

NOTE: For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate assessment does not need to be performed at the EOT Visit; the EOIV Visit will serve as the EOT Visit.

Clinical outcome categories are defined in Table 3 and microbiological outcome categories are defined in Table 4 in Section 4.2.3.2 – Rationale for Efficacy Endpoints.

The percentage of subjects with superinfection or new infection will also be estimated. Emergent infection categories are defined in Table 5 in Section 4.2.3.2 – Rationale for Efficacy Endpoints.

8.4.3 Pharmacokinetic Endpoints

Plasma concentration for ceftolozane, tazobactam, and tazobactam M1 will be determined. The data will be used to update the existing ceftolozane and tazobactam pediatric population PK models, which will be used to perform simulations to evaluate target attainment at suitable doses.

The PK target that best correlates with efficacy is % *f*T>MIC and % *f*T>Ct for ceftolozane and tazobactam, respectively. Therefore, in addition to plasma exposure (AUC_{0-8} and C_{max}), % *f*T>MIC and % *f*T>C_t will be derived for ceftolozane and tazobactam, respectively.

Plasma concentrations for tazobactam M1 will be reported separately.

8.5 Analysis Populations

8.5.1 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this trial. The ASaT population will consist of all randomized subjects who receive any amount of study treatment. Subjects will be included in the treatment arm corresponding to the IV study treatment they actually received, irrespective of the treatment to which they were randomized. If any subject receives study treatment from both treatment arms, he or she will be assigned to the treatment arm from which more study treatment was received.

8.5.2 Efficacy Analysis Populations

The efficacy analysis populations are defined in Table 10**.** Additional details about evaluability criteria for each efficacy analysis population will be provided in an evaluability guideline document.

Table 10 Efficacy Analysis Populations

Population[a]	Definition[a]
Modified Intent-to-Treat (MITT)	The MITT population will consist of all randomized subjects who receive any amount of study treatment. Subjects will be categorized based on the IV study treatment that subjects were randomized to, irrespective of what treatment they actually received.
Microbiological Modified Intent-to-Treat (mMITT)	The mMITT population will be the subset of subjects in the MITT population who have at least 1 pathogen identified from the baseline intra-abdominal culture, regardless of susceptibility to study treatment.
Clinically Evaluable (CE)	The CE population will be the subset of subjects in the MITT population who adhere to trial procedures and have a clinical outcome at the visit of interest. An interpretable culture is not required at the visit of interest. All subjects must have an evaluable clinical outcome at the visit of interest; subjects with an indeterminate clinical outcome are excluded from the CE population.
Microbiologically Evaluable (ME)	The ME population will be the subset of subjects in the CE population who have at least 1 causative pathogen identified from the baseline intra-abdominal culture.

[a] Additional details about evaluability criteria for each efficacy analysis population will be provided in an evaluability guideline document.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 - Statistical Methods.

8.6 Statistical Methods

8.6.1 Statistical Methods for Safety Analyses

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

The analysis of safety results for this trial will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. Based upon review of adult and pediatric trial safety data, no Tier 1 AEs of interest have been identified for this trial. Therefore, all safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment arm are provided for Tier 3 safety parameters.

Tier 2 endpoints for this trial include the percentage of subjects with AEs of elevated laboratory values, any AE, any treatment-related AE, any SAE, any AE that is both treatment-related and serious, and subjects who discontinued due to an AE. The 95% CIs will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the unstratified M&N method [20], an unconditional, asymptotic method.

Adverse events (specific preferred terms), system organ classes, or values outside of the local laboratory's reference range with at least 6 events in the experimental treatment arm and/or 2

events in the comparator treatment arm will be classified as belonging to Tier 2. Adverse events (specific preferred terms), system organ classes, or values outside of the local laboratory's reference range with frequencies less than these criteria in both treatment arms combined will be classified as belonging to Tier 3.

These thresholds were chosen because the 95% CI for the between-group difference in percentage will include zero when these thresholds are not met 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 between-group differences in AEs.

Continuous measures such as changes from baseline in laboratory parameter and vital sign values will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment arm in table format. In addition, summary statistics for both treatments will be provided. Safety summaries by treatment methods (IV study treatment or oral step-down therapy) and age groups will also be generated.

Missing safety parameters will be handled using the data as observed (DAO) approach, that is, any subject with a missing value will be excluded from the analysis. Change from baseline summaries require a baseline value. If a baseline value is missing, the latest pretreatment value will be used instead. If no pretreatment result is available, that subject will not be included in the summary. The safety summarization of results will be presented by treatment arm unless otherwise specified. Additional subgroup safety analysis summaries for the dosed subjects may be requested as needed.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	AEs of elevated laboratory values	X	X
	Any AE	X	X
	Any SAE	X	X
	Any treatment-related AE	X	X
	Any serious and treatment-related AE	X	X
	Discontinuation from trial treatment due to AE	X	X
	AEs (specific preferred terms), system organ classes, or values outside of the local laboratory's reference range with frequency ≥6 subjects in the experimental treatment arm and/or ≥2 subjects in the comparator treatment arm	X	X

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 3	AEs (specific preferred terms), system organ classes, or values outside of the local laboratory's reference range with frequency <6 subjects in the experimental treatment arm and frequency <2 subjects in the comparator treatment arm		X
	Change from baseline in laboratory parameter and vital sign values		X

AE = adverse event; CI = confidence interval; SAE = serious adverse event

8.6.2 Statistical Methods for Efficacy Analyses

For clinical and microbiological responses, missing data will be primarily handled with a treatment failure approach for the MITT and mMITT population and a DAO approach for the ME and CE populations (Table 12), with the following definitions:

- For the analysis of clinical response in the MITT and microbiological response in the mMITT population, subjects with missing clinical response or microbiological response (eg, indeterminate) will be considered treatment failures.
- For the analyses in the ME or CE population, subjects with a missing clinical response or microbiological response (eg, indeterminate) will be excluded from the population.
- A missing clinical outcome at the TOC Visit will be considered an indeterminate outcome unless the clinical outcome at the EOIV or EOT Visit is failure. A clinical response of failure at the EOIV or EOT Visit will be carried forward to the TOC Visit.
- A missing microbiological outcome at the TOC Visit will be considered indeterminate if the clinical outcome at the TOC Visit is indeterminate as well. Microbiological response will be presumed from clinical response when there is no suitable intra-abdominal specimen to culture on/after the EOT/EOIV Visit through the TOC Visit.

The M&N statistical method [20] with data stratified by age group will be used to make between-group comparisons for binary outcomes (Table 13), but no tests of hypotheses are planned in this estimation trial.

Table 12 Analysis Strategy for Efficacy Variables

Endpoint/Variable[a] (Description, Timepoint)	Primary (P) or Supportive (S) Approach	Analysis Population	Missing Data Approach
Secondary Endpoints			
Clinical success rate at the EOT and TOC Visits	P	MITT	Treatment Failure
	S	mMITT	Treatment Failure
	S	CE	Data As Observed
Per-subject microbiological eradication rate at the EOT and TOC Visits	P	mMITT	Treatment Failure
	S	ME	Data As Observed
Exploratory Endpoints			
Clinical success rate at the EOIV Visit	P	MITT	Treatment Failure
	S	mMITT	Treatment Failure
	S	CE	Data As Observed
Per-subject microbiological eradication rate at the EOIV Visit	P	mMITT	Treatment Failure
	S	ME	Data As Observed
Per-pathogen microbiological eradication rate at the EOIV, EOT, and TOC Visits	P	mMITT	Treatment Failure
	S	ME	Data As Observed

CE = clinically evaluable; EOIV = End of IV Treatment; EOT = End of Treatment; ME = Microbiologically Evaluable; MITT = Modified Intent-to-Treat; mMITT = microbiological Modified Intent-to-Treat; TOC = Test of Cure

[a] The Miettinen and Nurminen statistical method [20] will be used for all analyses and will include stratification by age.

NOTE: For subjects who receive IV study treatment only (without optional oral step-down therapy), a separate assessment does not need to be performed at the EOT Visit; the EOIV Visit will serve as the EOT Visit.

Table 13 Estimated Two-sided 95% Confidence Intervals Based on Different Assumed Observed Rates of Efficacy Endpoints

Same Observed Clinical Success or Per-subject Microbiological Response Rate Across Both Arms	Ceftolozane/tazobactam (n=90)	Meropenem (n=30)	Estimate (95% CI)
70%	63 (70.0%)	21 (70.0%)	0.00 (-17.20, 20.08)
80%	72 (80.0%)	24 (80.0%)	0.00 (-14.50, 18.88)
90%	81 (90.0%)	27 (90.0%)	0.00 (-10.60, 16.46)

CI = confidence interval

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Analyses of Baseline Characteristics and Demographics

No statistical hypothesis tests will be performed on demographic and baseline characteristics. The number and percentage of subjects screened, randomized/allocated, the primary reasons for screening failure, and the primary reasons for discontinuation will be displayed. Demographic variables (as follows), baseline characteristics, primary diagnosis, prior and concomitant therapies, and medical history will be summarized by treatment using descriptive statistics for continuous or categorical variables, as appropriate. Summaries of baseline pathogens and signs and symptoms will also be provided.

Demographic variables include but are not limited to the following: Age, sex, race, body weight, body mass index, and geographic region of enrollment.

Baseline characteristics include but are not limited to the following:

- CrCL group (<50 mL/min, ≥50 to <80 mL/min, ≥80 mL/min)
- Baseline diagnosis
- Baseline signs and symptoms of cIAI
- Primary site of infection
- Anatomic site of infection
- Presence of abscess
- Number of abscesses (single, multiple)
- Presence of peritonitis (yes, no)
- Peritonitis type
- Localized complicated appendicitis (yes, no)
- Etiological mechanism
- Failure of prior therapy
- Procedure type
- Wound closure
- All abscesses confirmed drained (yes, no)
- Site of infection (appendix, nonappendix)

- Prior antibiotic use
- Presence of bacteremia at baseline (yes, no)
- Number of baseline pathogens (polymicrobial, monomicrobial)
- ESBL status of Enterobacteriaceae (ESBL, non-ESBL)
- AmpC overexpression status

In addition, for randomized subjects, baseline characteristics will be presented by age category and treatment arm.

8.6.3.2 Population Pharmacokinetic Analyses

Based on PK data obtained within this study, a separate population PK analysis will be performed for ceftolozane and tazobactam. The prospective details of this analysis will be specified in a separate population PK analysis plan and the results will be included in a separate report.

8.7 Interim Analyses

No interim analyses for efficacy are planned for this trial. However, an external DMC will convene to review combined safety data from the present trial and the companion Phase 2 trial in pediatric subjects with cUTI (MK-7625A-034). Additional details are available in the external DMC charter.

8.8 Multiplicity

There will be no multiplicity adjustments in the analyses of this estimation trial.

8.9 Sample Size and Power Calculations

This is an estimation trial; no formal statistical testing will be performed for the efficacy or safety endpoints. In this trial, approximately 240 subjects (combined across MK-7625A-034 and MK-7625A-035) will be enrolled with an expected 180 subjects in the ceftolozane/tazobactam plus metronidazole treatment arm and an expected 60 subjects in the meropenem plus placebo treatment arm. With a sample size of 180 ceftolozane/tazobactam-treated subjects in both this trial and the tandem cUTI trial (MK-7625A-034) (Section 4.2.1.1 – Rationale for Sample Size), AEs with an underlying true incidence of at least 2% in the treatment arm are anticipated to occur with a probability of at least 97%.

The primary objective of this trial is assessment of the accumulated safety data. Trial-specific safety assessments are described in Section 8.6.1 – Statistical Methods for Safety Analyses; however, safety data will be combined across MK-7625A-034 and MK-7625A-035. Table 14 shows estimated treatment differences and associated 2-sided 95% CIs for events under varying assumptions of the observed number of subjects having a certain event combined across trials. These calculations are based on the unstratified M&N method [20].

Table 14 Estimated Treatment Differences and Two-sided 95% Confidence Intervals

Same Expected Event Rate Across Both Treatment Groups	Ceftolozane/tazobactam (n=180)	Meropenem (n=60)	Estimate (95% CI)
2%	4 (2.2%)	2 (3.3%)	-1.1 (-9.30, 3.05)
4%	8 (4.4%)	4 (6.7%)	-2.2 (-1.18, 3.57)
10%	18 (10.0%)	6 (10.0%)	0.0 (-10.80, 7.64)
15%	28 (15.6%)	10 (16.7%)	-1.1 (-13.42, 8.53)

CI = confidence interval

NOTE: Given the same expected event rate across both treatment groups, treatment difference estimates are not always zero given the discrete nature of events. The number of events within each treatment group is selected based on the minimum number of events required to match or exceed the expected event rate across both groups.

8.10 Subgroup Analyses

To assess the consistency of clinical and microbiological response at the EOT and TOC Visits, the response rates with 95% CIs will be estimated for each treatment arm within each category listed below.

- Age category (birth to <3 months, 3 months to <2 years, 2 years to <6 years, 6 years to <12 years, 12 years to <18 years)
- Sex (male, female)
- Region of enrollment
- Duration of IV study treatment
- Primary site of infection (bowel [small or large], other site of infection)
- Etiological mechanism (nosocomial infection [postoperative/hospital acquired infection], community-acquired infection [trauma, spontaneous rupture, malignancy or other])
- Number of abscesses (single, multiple)
- Peritonitis type (local, diffuse)
- Procedure type (percutaneous aspiration, laparoscopy, laparotomy, other)
- Prior antibiotic use (yes, no)
- Site of infection (appendix, nonappendix)
- Baseline bacteremia (yes, no)

- Number of baseline pathogens (polymicrobial, monomicrobial)
- Pathogen MIC (susceptible, intermediate, resistant as defined in the SAP) and pathogen classification
- ESBL status of Enterobacteriaceae (ESBL, non-ESBL)
- AmpC overexpression status

Additional subgroup analysis summaries for randomized subjects with regard to other factors may be considered as needed.

8.11 Compliance (Medication Adherence)

Each subject will be scheduled to receive IV study treatment every 8 hours (3 times daily) for at least 9 doses. After that, subjects may be switched to open-label, standard of care oral step-down antibiotic therapy at the investigator's discretion. Oral step-down therapy is considered study treatment. The total duration of study treatment (IV only or IV + oral) is a minimum of 7 days and a maximum of 14 days.

In this study, the dosing of IV study treatment will be documented in the study intervention CRF page by recording the date, time, and whether or not each dose of IV study treatment was completely infused. The amount of oral step-down therapy taken by each subject will be recorded in the concomitant medication CRF page. This information will be used to calculate the IV study treatment and overall study treatment compliance rates. Details of the compliance calculations will be provided in the sSAP and/or CSR.

8.12 Extent of Exposure

The extent of exposure during IV study treatment and the total study treatment exposure will be summarized as both continuous and categorical variables alongside counts and percentages for the "Number of Days on Therapy" by treatment arm in the ASaT population. The summary of exposure by treatment arms and age group will also be provided.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 15.

Table 15 Product Descriptions

Treatment Group	Product Name and Dosage Form	Dose	Potency	Total Dosage Forms	Additional Information
1	Ceftolozane/ tazobactam-IV	Cohort dose	1 g/0.5 g	1.5 g/vial	Commercial Zerbaxa product – clinically labeled
1	Metronidazole-IV	Cohort dose	0.5 g	0.5 g/ 100-mL bag or 0.5 g/vial	Commercial metronidazole product – clinically labeled
2	Meropenem-IV	Cohort dose	1.0 g	1.0 g/vial	Commercial meropenem product – clinically labeled

Product Name & Potency	Dosage Form	Source/Additional Information
Ceftolozane 1 g/ tazobactam 0.5 g	1 g/0.5 g lyophilized vial	Provided centrally by the Sponsor
Metronidazole 0.5 g	0.5 g/100-mL bag or 0.5 g/vial	Provided centrally by the Sponsor
Meropenem 1 g	1-g lyophilized vial	Provided centrally by the Sponsor
Placebo	IV	Site sourced

All supplies indicated in Table 15 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 15 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

The clinical supplies will be open-labeled and each vial/dosage form will contain a component identification (CID) number for management of the supplies through an IVRS/IWRS. Subjects will receive the IV study treatment following preparation by an unblinded pharmacist (Section 5.2.6 – Trial Blinding), for a maximum of 14 days. The subject's parent (or guardian) will remain blinded to the IV study treatment that the subject receives. Importantly, the unblinded pharmacist will be uninvolved in any of the postinfusion evaluations for the subject. All study personnel involved with the postinfusion evaluations of

safety and efficacy outcomes, including the study coordinator(s), investigator, or subinvestigator(s), must have no access to the treatment group assignment or the preparation of the study infusion.

9.3 Clinical Supplies Disclosure

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

See Section 7.1.4.4, Subject Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign study treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 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 institutional review board, ethics review committee (IRB/ERC) 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 trial 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.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By providing documented informed consent, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject 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 subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. 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.

10.2 Compliance with Financial Disclosure Requirements

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.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial 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 trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial 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 trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

[1] 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.

[2] Thompson AE, Marshall JC, Opal SM. Intraabdominal infections in infants and children: descriptions and definitions. Pediatr Crit Care Med. 2005 May;6(3 Suppl):S30-5.

[3] Claud EC. Neonatal necrotizing enterocolitis -inflammation and intestinal immaturity. Antiinflamm Antiallergy Agents Med Chem. 2009 Sep;8(3):248-259.

[4] Newman N, Wattad E, Greenberg D, Peled N, Cohen Z, Leibovitz E. Community-acquired complicated intra-abdominal infections in children hospitalized during 1995-2004 at a paediatric surgery department. Scand J Infect Dis. 2009;41(10):720-6.

[5] Nance ML, Adamson WT, Hedrick HL. Appendicitis in the young child: a continuing diagnostic challenge. Pediatr Emerg Care. 2000 Jun;16(3):160-2.

[6] Sartelli M, Catena F, Coccolini F, Pinna AD. Antimicrobial management of intra-abdominal infections: literature's guidelines. World J Gastroenterol. 2012 Mar 7;18(9):865-71.

[7] Brook I. Bacterial studies of peritoneal cavity and postoperative surgical wound drainage following perforated appendix in children. Ann Surg. 1980 Aug;192(2):208-12.

[8] Dupont H. The empiric treatment of nosocomial intra-abdominal infections. Int J Infect Dis. 2007 May;11 Suppl 1:S1-6.

[9] Spirt MJ. Complicated intra-abdominal infections: a focus on appendicitis and diverticulitis. Postgrad Med. 2010 Jan;122(1):39-51.

[10] Goldin AB, Sawin RS, Garrison MM, Zerr DM, Christakis DA. Aminoglycoside-based triple-antibiotic therapy versus monotherapy for children with ruptured appendicitis. Pediatrics. 2007 May;119(5):905-11.

[11] Bradley JS, Ang JY, Arrieta AC, Larson KB, Rizk ML, Caro L, et al. Pharmacokinetics and safety of single intravenous doses of ceftolozane/tazobactam in children with proven or suspected Gram-negative infection. Pediatr Infect Dis J. 2018 Nov;37(11):1130-6.

[12] Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009 Mar;20(3):629-37.

[13] Craig W, Andes D. In Vivo Activities of Ceftolozane, a New Cephalosporin, with and without Tazobactam against Pseudomonas aeruginosa and Enterobacteriaceae, Including Strains with Extended-Spectrum -Lactamases, in the Thighs of Neutropenic Mice. Antimicrob Agents Chemother 2013, 57(4): p. 1577–1582

[14] Xiao AJ, Caro L, Popejoy MW, Huntington JA, Kullar R. PK/PD Target Attainment With Ceftolozane/Tazobactam Using Monte Carlo Simulation in Patients With Various Degrees of Renal Function, Including Augmented Renal Clearance and End-Stage Renal Disease. Infect Dis Ther. 2016 Dec 24. doi: 10.1007/s40121-016-0143-9.

[15] Cohen-Wolkowiez M, Poindexter B, Bidegain M, Weitkamp JH, Schelonka RL, Randolph DA, et al. Safety and effectiveness of meropenem in infants with suspected or complicated intra-abdominal infections. Clin Infect Dis. 2012 Dec;55(11):1495-502.

[16] Pickering LK, Baker CJ, Kimberlin DW, Long SS. Red Book: 2012 Report of the committee on infectious diseases. Clostridium difficile. 29 ed. Elk Grove Village: American Academy of Pediatrics, 2012:285-7.

[17] U.S. Prescribing Information: MERREM I.V. (meropenem for Injection): 2013.

[18] Smith PB, Cohen-Wolkowiez M, Castro LM, Poindexter B, Bidegain M, Weitkamp JH, et al. Population pharmacokinetics of meropenem in plasma and cerebrospinal fluid of infants with suspected or complicated intra-abdominal infections. Pediatr Infect Dis J. 2011 Oct;30(10):844-9.

[19] Lee LS, Kinzig-Schippers M, Nafziger AN, Ma L, Sörgel F, Jones RN, Drusano GL, Bertino JS Jr. Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. Diagn Microbiol Infect Dis. 2010 Nov;68(3):251-8.

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

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, 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 subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

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 Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. 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 of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. 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. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

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

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects 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. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck 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

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

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

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

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

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

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Approximate Blood Volumes Drawn/Collected by Trial Visit

The approximate maximum blood volumes to be collected at each trial visit are summarized in Table 16.

Table 16 Approximate Blood Volumes Collected by Trial Visit

	Approximate Blood Sample Volume (mL)						
Trial Period:	**Screening**	**Treatment (5 to 14 days)**				**Follow-up**	
Visit Number:	**1**	**3 to 16**	**17**	**18**	**19**	**20**	**21**
Trial Visit:	**Screening**	**IV Clinical Assessments**	**EOIV (all subjects)**	**Oral Clinical Assessment (only for IV to oral switch)**	**EOT only for IV to oral switch)**	**TOC (all subjects)**	**LFU[a] (all subjects)**
Safety hematology and chemistry, serum creatinine	3.5	3.5[b]	3.5	3.5	3.5	3.5	3.5[c,d]
Coombs test (direct)	1.0	0	1.0	0	0	0	0
Serum pregnancy test[e]	3.0	0	0	0	0	3.0[e]	0
Blood for culture	7.0[c]	7.0[c,f]	0	0	0	0	0
Blood for PK analyses (Day 3 only)[g]	0	0.75 [g]	0	0	0	0	0
Maximum expected total blood volume	14.5	11.25	4.5	3.5	3.5	6.5	3.5

EOIV = End of IV Treatment; EOT = End of Treatment; IV = intravenous; LFU = Last Follow-up; PK = pharmacokinetics; TOC = Test of Cure

[a] At the discretion of the investigator, the LFU Visit may be conducted by telephone, unless the subject has abnormal laboratory values or AEs that require follow-up.

[b] To be completed on Day 3 and then once weekly while the subject is receiving IV study treatment.

[c] If clinically indicated.

[d] To be performed only if LFU Visit is conducted in person instead of by telephone.

[e] Female subjects of childbearing potential only. A urine pregnancy test instead of a serum pregnancy test may be performed at the TOC Visit, if deemed clinically appropriate by the investigator.

[f] Blood samples for culture should be collected if signs of sepsis appear at any time during the study.

[g] Blood samples for ceftolozane, tazobactam, and tazobactam M1 concentration assays will be collected from all subjects over one 8-hour dosing period on Day 3 of the treatment period after administration of at least 6 doses of IV study treatment (see Section 7.1.3.6 – Pharmacokinetic Evaluations).

12.3 List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition
%CV	Coefficient of variation
% *f*T>MIC	Percentage of dosing interval during which free concentration of drug (ceftolozane) exceeds the MIC
% *f*T>Ct	Percentage of dosing interval during which free concentration of drug (tazobactam) exceeds the Ct
AE	Adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BLI	β-lactamase inhibitor
BP	Blood pressure
CE	Clinically evaluable
CI	Confidence interval
cIAI	Complicated intra-abdominal infection
CID	Component identification
CL	Clearance
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum observed concentration
CrCL	Creatinine clearance
CRF	Case Report Form
CSR	Clinical study report
Ct	Threshold drug concentration
CT	Computed tomography
cUTI	Complicated urinary tract infection
DAO	Data as observed
DMC	Data Monitoring Committee
eCRF	Electronic case report form

Abbreviation or Term	Definition
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Association
EOC	Executive Oversight Committee
EOIV	End of IV Treatment (Visit)
EOT	End of Treatment (Visit)
ERC	Ethics Review Committee
ESBL	Extended-spectrum β- lactamase
EU	European Union
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act
GCP	Good Clinical Practice
GI	Gastrointestinal
Hg	Mercury (for BP, mm Hg)
HIV	Human immunodeficiency virus
IAI	Intra-abdominal infection
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDSA	Infectious Disease Society of America
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Integrated web response system
LFU	Last Follow-up (Visit)
M&N	Miettinen and Nurminen (statistical method)
MDR	Multidrug-resistant
ME	Microbiologically evaluable
MIC	Minimum inhibitory concentration
MITT	Modified Intent-to-Treat
mMITT	Microbiological Modified Intent-to-Treat
MRI	Magnetic resonance imaging

Abbreviation or Term	Definition
MRSA	Methicillin-resistant *Staphylococcus aureus*
NEC	Necrotizing enterocolitis
NP	Nosocomial pneumonia
OTC	Over the counter
PIN	Personal identification number
PK	Pharmacokinetic(s)
PTA	Probability of target attainment
Q	Intercompartmental clearance
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard operating procedure
sSAP	Supplemental Statistical Analysis Plan
T>MIC	Time above MIC
$t_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TOC	Test of Cure (Visit)
ULN	Upper limit of normal
US	United States (of America)
UTI	Urinary tract infection
Vc	Central volume of distribution
Vp	Peripheral volume of distribution
WBC	White blood cell

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	