**Safety and Efficacy of Ceftolozane/Tazobactam Plus Metronidazole Versus Meropenem From a Phase 2, Randomized Clinical Trial in Pediatric Participants With Complicated Intra-abdominal Infection**

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## Supplemental Digital Content 1

## Supplemental Methods

Inclusion and Exclusion Criteria for Study Eligibility

**Inclusion Criteria**

- Had a legal representative provide written informed consent for the study on the participant's behalf and provide age-appropriate written informed assent (as applicable)
- Was male or female from birth (defined as >32 weeks gestational age and ≥7 days postnatal) to <18 years of age
    - In Ukraine, enrollment age of male or female participants was limited to 2 to <18 years; participants <2 years of age were not permitted to enroll
- Was able to comply with the protocol for the duration of the study
- Required 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 following criteria:
        - Clinical evidence of cIAI as indicated by 1 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; *and*
        - Radiographic evidence consistent with cIAI
- Had 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 (participants with a diagnosis of NEC were exempt from this inclusion criteria and were not required to have surgery planned or completed in order to be eligible for enrollment)
- Had baseline intra-abdominal specimen collection in compliance with the protocol; participants enrolled preprocedure were to have a sample obtained during the interventional procedure (participants with NEC who did not require surgical intervention were exempt from this inclusion criteria and were not required to have an intra-abdominal culture)

- Was a female or a male who was not of reproductive potential or, if of reproductive potential, agreed to avoid becoming pregnant or impregnating a partner during screening, while receiving study treatment, and for ≥30 days after the last dose of study treatment
- The participant was a female of reproductive potential who was not pregnant, not planning to become pregnant within 30 days of the last day of study treatment administration, and was nonlactating

**Exclusion Criteria**

- Was currently participating in or had participated in an interventional clinical study with an investigational compound or device within 30 days before the first dose of study treatment in this current study
- Had previously participated in any study of ceftolozane or ceftolozane/tazobactam or had enrolled previously in the current study and had been discontinued
- Had a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that, in the opinion of the investigator, might have exposed the participant to increased risk by participating in the study, confounded the results of the study, or interfered with the participant's participation for the full duration of the study
- Had a history of any moderate or severe hypersensitivity, allergic reaction, or other contraindication to a β-lactamase antibiotic, BLI, or metronidazole
- Had an IAI within the past 1 year before randomization that was caused by a pathogen known to be resistant to either IV study treatment
- Had a concomitant infection at the time of randomization that required nonstudy systemic antibacterial therapy in addition to IV study treatment or oral step-down therapy (medications with only gram-positive activity [eg, vancomycin, linezolid] were permitted)
- Had received potentially therapeutic antibacterial therapy (eg, with gram-negative activity) for a duration of >24 hours during the 48 hours preceding the first dose of study treatment, unless the participant was considered to be failing antibiotic therapy for cIAI
    - A participant who was considered to be failing a previous antibiotic regimen was required to meet all of the following criteria:
        - Had received the systemic antibacterial treatment for ≥48 hours
        - Had clinical and operative or radiographic findings clearly indicating ongoing infection
        - Had planned operative intervention ≤24 hours after the first dose of study treatment
        - Had not received any further nonstudy antibiotics postoperatively
- Had any of the following conditions, current devices, or procedures as noted in the protocol:
    - Intractable cIAI that the investigator anticipated would require >14 days of study treatment
    - Abdominal wall abscess
    - Small bowel obstruction
    - Ischemic bowel disease without perforation
    - Traumatic bowel perforation with surgery within 12 hours of perforation

- Perforation of gastroduodenal ulcers requiring surgery within 24 hours of perforation (these were considered situations of peritoneal soiling before the infection had become established)
- Suspected uncomplicated IAI (eg, cholecystitis without rupture or extension beyond the gallbladder wall)
- Acute suppurative cholangitis
- Infected necrotizing pancreatitis
- Pancreatic abscess

- Had moderate or severe impairment of renal function, defined as an estimated CrCl <50 mL/min/1.73 $m^2$ based on the revised Schwartz equation or requirement for peritoneal dialysis, hemodialysis, or hemofiltration
- Had 1 or more of the laboratory abnormalities as noted in the protocol in a specimen obtained at baseline:
  - ANC <1000/$mm^3$
  - AST or ALT ≥3 × ULN
  - Total bilirubin ≥2 × ULN (if 7 to ≤28 days of age and breastfeeding, total bilirubin >10 mg/dL or ≥2 × ULN)
- Had a seizure disorder or was anticipated to be treated with divalproex sodium or valproic acid during the course of study treatment
- Was receiving or expected to receive immunosuppressive agents, probenecid, valproic acid, disulfiram, ergot derivatives, or nonstudy systemic (IV or oral) antibacterial treatments
  - Participants could have empiric enterococcal coverage for the index cIAI with an enterococcal antibiotic with activity limited to gram-positive coverage, and 1 dose of prophylactic antibiotic with gram-negative activity was allowed
  - Participants could have empiric antifungal coverage for the index cIAI with an azole, echinocandin, or polyene antifungal based on local standard of care
- Had any rapidly progressing disease or immediately life-threatening illness, including hepatic failure, respiratory failure, or septic shock
- Had an immunocompromising condition or receipt of immunosuppressive therapy (short-term treatment with systemic [IV or oral] steroids of <1 week duration was allowed, as was topical steroids for treatment of a skin condition)
- Had a history of malignancy ≤5 years before signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer
- Had planned receipt of suppressive/prophylactic antibiotics with gram-negative activity after completion of study treatment
- Was or had an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who was investigational site or sponsor staff directly involved with this study

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BLI, β-lactamase inhibitor; cIAI, complicated intra-abdominal infection; CrCl, creatinine clearance; IAI, intra-abdominal infection; IV, intravenous; NEC, necrotizing enterocolitis; ULN, upper limit of normal.

Blinding and Randomization

This trial was conducted as a double-blind trial. The final database was not unblinded until after medical/scientific review was performed, protocol deviations were identified, and data were declared final and complete. Participants were randomized to IV ceftolozane/tazobactam plus metronidazole or meropenem plus placebo in a 3:1 ratio using a central interactive voice response system/integrated web response system. Ceftolozane/tazobactam and meropenem were packaged identically so that masking was maintained, and infusion bags, IV lines, and any other dispensing devices were covered as needed to maintain masking.

Specimen Collection

Sterilely collected fluid aspirates or tissue/biopsy samples were recommended, and swabs of purulent material were discouraged. Thereafter, specimens for culture were obtained from the site of infection, if clinically indicated (eg, if re-intervention was required, collection during the additional surgery in participants with clinical failure) for microbiologic assessment.

At the central laboratory, isolates were identified using matrix-assisted laser desorption ionization-time of flight mass spectrometry and susceptibility tested by reference broth microdilution against ceftolozane/tazobactam and meropenem.