**Supplemental Digital Content 1. Methods**

Inclusion and Exclusion Criteria for Study Eligibility

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| **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) for the trial
* Was male or female from birth (defined as >32 weeks gestational age and ≥7 days

postnatal) to <18 years of age* + In Ukraine, enrollment was limited to participants who were 3 months to <18 years of age
* Was able to comply with the protocol for the duration of the study
* Required IV antibacterial therapy for the treatment of cUTI
* Had a pretreatment baseline urine culture specimen obtained within 48 hours before the start of administration of the first dose of study treatment and preferably before administration of any potentially therapeutic antibacterial agents
* Specimen was obtained by suprapubic aspiration, clean intermittent urethral catheterization, indwelling urethral catheter, or midstream clean catch
* Participants may have been enrolled in this study and started IV study treatment before the investigator knew the results of the baseline urine culture; however, participants without documented ≥105 CFU/mL of an appropriate gram-negative uropathogen cultured from a baseline urine specimen were required to discontinue study treatment immediately after culture result
* Had pyuria, defined as follows:
* If ≥1 year of age: WBC count >10 cells/μL in unspun urine or ≥10 cells/high-power field in spun urine
* If <1 year of age: WBC count >5 cells/μL in unspun urine or ≥5 cells/high-power field in spun urine
* Had clinical signs and/or symptoms of cUTI (pyelonephritis or cLUTI) at the

screening visit* For pyelonephritis, participants must have had ≥2 of the following new or worsening signs and/or symptoms:
* If 0 to <2 years of age:
* Fever (as defined by the investigator)
* Failure to thrive
* Recent weight loss
* Irritability
* Poor feeding
* Lack of normal level of activity
* Abdominal tenderness on physical examination
* Vomiting
* Jaundice
* If 2 to <18 years of age:
* Fever (as defined by the investigator)
* Dysuria
* Urinary urgency
* Urinary frequency
* New-onset urinary incontinence
* Suprapubic pain, flank pain, or abdominal pain
* Suprapubic tenderness or CVA tenderness on physical examination
* Nausea or vomiting

OR* For cLUTI, participants must have ≥2 of the new or worsening signs and/or symptoms listed above AND must have ≥1 of the following complicating factors:
* Obstructive uropathy
* Congenital, functional, or anatomic abnormality of the urogenital tract
* Temporary indwelling urinary catheter
* Bladder instrumentation within <24 hours
* Recurrent UTI (≥2 events within a 12-month period)
* 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
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| **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 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 expose the participant to increased risk by participating in the study, confound the results of the study, or interfere with the participant’s participation for the full duration of the study
* Had a history of any moderate or severe hypersensitivity (eg, anaphylaxis), allergic reaction, or other contraindication to any of the following: β-lactam antibacterial agents (eg, penicillins, cephalosporins, and carbapenems), or β-lactamase inhibitors (eg, tazobactam, sulbactam, clavulanic acid, and avibactam)
* A history of mild rash to any of these agents is not a contraindication to enrollment
* Had a history of a cUTI within the past 1 year before randomization that is 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 allowed)
* Had received potentially therapeutic antibacterial therapy (eg, with gram-negative activity), including bladder infusions with topical urinary antiseptics or antibacterial agents, for a duration of >24 hours during the 48 hours preceding the first dose of study treatment
* Provided all other eligibility criteria were met, including obtaining a baseline study-qualifying urine culture, the following participants could be enrolled; however, participants without documented ≥105 CFU/mL of an appropriate gram-negative uropathogen were required to discontinue study treatment immediately after culture results:
* Participants with an active cUTI who received ≥48 hours of a prior antibacterial regimen, if in the opinion of the investigator, there is evidence they were failing the prior antibacterial regimen
* Participants who were receiving antibacterial prophylaxis for cUTI who presented with signs and symptoms consistent with an active new cUTI due to an appropriate gram-negative uropathogen
* Had any of the following:
* Intractable UTI or pyelonephritis infection at baseline that the investigator anticipated would require >14 days of study treatment
* Confirmed fungal urinary tract infection at time of randomization with ≥103 fungal CFU/mL
* Permanent indwelling bladder catheter or instrumentation, including nephrostomy
* Current urinary catheter that is not scheduled to be removed before the end of all study treatment (intermittent straight catheterization during the study treatment period is acceptable)
* Complete, permanent obstruction of the urinary tract
* Suspected or confirmed perinephric or intrarenal abscess
* Documented ileal loop reflux
* Suspected or confirmed prostatitis, urethritis, or epididymitis
* Trauma to pelvis/urinary tract
* Had severe impairment of renal function, defined as an estimated CrCl <50 mL/min/1.73 m2 based on the Schwartz equation [23] or requirement for peritoneal dialysis, hemodialysis, or hemofiltration
* Had 1 or more of the following laboratory abnormalities in a specimen obtained at baseline:
* ANC <1000/mm3
* 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 is anticipated to be treated with divalproex sodium or valproic acid during the course of study treatment
* Had any rapidly progressing disease or immediately life-threatening illness, including acute hepatic failure, respiratory failure, or septic shock
* Had an immunocompromising condition, including established AIDS, hematologic malignancy, or bone marrow transplantation, or immunosuppressive therapy including cancer chemotherapy, medications for prevention of organ transplantation rejection, or the administration of corticosteroids equivalent to or greater than the systemic equivalent of ≥2 mg/kg total daily dose of prednisone for >14 days in the 30 days preceding randomization
* 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
* Planned receipt of suppressive/prophylactic antibacterial agents with gram-negative activity after completion of study treatment
* Based on site level standard of care, participants at increased risk of recurrent pyelonephritis or cUTI (eg, vesico-ureteral reflux grade 3 through 5), wherein there was a clear benefit to low-dose antibacterial prophylaxis, were permitted
* Was or had an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or sponsor staff directly involved with this study
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ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotranferase; CFU, colony-forming unit; cLUTI, complicated lower urinary tract infection; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; CVA, costovertebral angle; IV, intravenous; ULN, upper limit of normal; UTI, urinary tract infection; WBC, white blood cell.

Sample Size Calculation

The sample size for this study was based on enrollment of approximately 180 participants receiving ceftolozane/tazobactam in the combined safety analysis population of this study (MK-7625A-034; NCT03230838) and the study in pediatric complicated intra-abdominal infection (MK-7625A-035; NCT03217136), which would allow for a 97.3% probability of detecting adverse events (AEs) with an underlying true incidence of ≥2% within the ceftolozane/tazobactam treatment group. Ultimately, 170 participants were enrolled in the ceftolozane/tazobactam treatment group of the combined studies, which allowed for a 96.7% probability of detecting an AE with an underlying true incidence of ≥2%. Decreasing enrollment did not negatively impact the key goals or scientific validity of the studies and allowed for sufficient data to evaluate safety, efficacy, and pharmacokinetics in both study populations.

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 and Culture of Urine Specimens

The use of sterile urine collection bags was allowed for young children who were unable to provide midstream clean-catch urine specimens at postbaseline visits. Urine specimens obtained from urinary bags were not permitted, but collection from indwelling urethral catheters was permitted. If pyuria was not present, any bacterial growth in these samples was considered to be a contaminant.
Culture of the urine specimen, isolation of pathogen(s), initial identification of pathogen(s), and susceptibility testing were conducted by local laboratories. Isolates were submitted to a central laboratory for identification and evaluation of antibacterial susceptibility profiles using the Clinical and Laboratory Standards Institute (CLSI) reference testing methodology and quality control recommendations.1 The isolates that displayed predefined minimum inhibitory concentration criteria were screened for the presence of ESBL-encoding genes.
Baseline study-qualifying urine cultures must have contained 1 and not more than 2 gram-negative bacterial isolates at ≥105 colony-forming units/mL each. If >2 bacterial isolates were identified from a single urine specimen for noncatheterized participants or if >1 bacterial isolate was identified for catheterized participants, the culture was deemed contaminated unless a pathogen yielding ≥105 colony-forming units/mL from urine was also isolated from the blood culture at the screening visit. Coagulase-negative *Staphylococci* and nongroup D *Streptococci* were not considered causative pathogens in this study.

End Point Definitions

Clinical cure was defined as complete resolution or marked improvement in signs and symptoms of the complicated urinary tract infection (cUTI) or return to pre-infection signs and symptoms, such that no further antibacterial therapy is required. Clinical failure was defined as any of the following: persistence or reappearance of 1 or more sign or symptom of infection that requires alternative nonstudy treatment for the current cUTI, new signs or symptoms of infection that require alternative nonstudy treatment of a cUTI due to an appropriate gram-negative uropathogen, requirement of antibacterial therapy beyond the protocol-defined treatment duration of 14 days, or death related to cUTI.

Microbiologic eradication was defined as a postbaseline urine culture showing all uropathogens found at baseline at ≥105 colony-forming units (CFU)/mL reduced to <104 CFU/mL. Presumed eradication was defined as an absence of material to culture in a participant who is assessed as having partial improvement or clinical cure. Persistence was defined as a postbaseline urine culture in which the uropathogen(s) found at baseline at ≥105 CFU/mL persist(s) at ≥104 CFU/mL. Indeterminate was defined as no appropriate urine culture result available. Per-pathogen microbiologic outcome was determined for each uropathogen isolated from a baseline study-qualifying culture, with eradication (as defined above) considered a favorable microbiologic response.

Composite cure was defined as a clinical response of success and per-participant microbiologic response of eradication. Composite failure was defined as a clinical response of failure and/or per-participant microbiologic response of persistence. If one of the outcomes was failure (clinical) or persistence (microbiologic) and the other was indeterminate, the composite response of the participant was considered failure. Composite response was considered indeterminate if clinical response was indeterminate and/or per-participant microbiologic response was indeterminate. If one of the outcomes was clinical success or microbiologic eradication and the other was indeterminate, the composite response of the participant was considered indeterminate.

Concomitant Treatments

Concomitant systemic antibacterial agents with gram-negative activity, other than 1

dose of a prophylactic antibacterial agent, were not permitted while the subject was receiving IV study treatment or oral step-down therapy. Bladder infusions with topical urinary antiseptics or antibacterial agents were not permitted.

**REFERENCES**

1. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial

susceptibility testing, 30th edition. January 2020. Available at: https://www.nih.org.pk/wpcontent/uploads/2021/02/CLSI-2020.pdf. Accessed November 30, 2021.