Official Title:	**A Phase 3, randomized, double-blind, double-dummy, multicenter, multinational study to assess the efficacy and safety of orally administered tebipenem pivoxil hydrobromide (TBP-PI-HBr) compared to intravenously administered imipenem-cilastatin in patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP)**
NCT Number:	**NCT06059846**
Document Date:	**Protocol Version 4.1: 26 August 2024**

Clinical Study Protocol

PROTOCOL NUMBER:	SPR994-305
PROTOCOL TITLE:	A Phase 3, randomized, double-blind, double-dummy, multicenter, multinational study to assess the efficacy and safety of orally administered tebipenem pivoxil hydrobromide (TBP-PI-HBr) compared to intravenously administered imipenem-cilastatin in patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP)
PROTOCOL NAME:	PIVOT-PO
INVESTIGATIONAL AGENT DRUG (*Active*):	Tebipenem pivoxil hydrobromide (TBP-PI-HBr, previously known as SPR994)
SPONSOR NAME AND ADDRESS:	Spero Therapeutics, Inc. 675 Massachusetts Ave. Cambridge, MA 02139, USA
EU CT NUMBER:	2023-503785-22-00
ClinicalTrials.gov ID	NCT06059846
IND:	132744
MEDICAL EXPERT/QUALIFIED PHYSICIAN NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER:	[redacted], MD Sponsor Medical Monitor 675 Massachusetts Ave Cambridge, MA 02139 USA [redacted]
SPONSOR REPRESENTATIVE AUTHORIZED TO SIGN PROTOCOL:	[redacted], MD [redacted] Spero Therapeutics, Inc.
CLINICAL LABORATORIES/ BIOANALYTICAL FACILITY:	**Clinical Laboratories:** ICON Laboratory Services Inc. South County Business Park Leopardstown Dublin 18, Ireland Tel: +353 1 2912409 **Bioanalytical Laboratories:** Keystone Bioanalytical, Inc. 501 Dickerson Road North Wales, PA 19454 USA Tel: (215) 699-8885 Charles River Laboratories, Inc. 334 South St., Shrewsbury, MA 01545 USA Tel: (508) 753-5000
DATE:	26Aug2024

GCP Statement: This study is to be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), EU CT Regulation 536/2014, and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.
Confidentiality Statement: Information contained in this protocol should not be disclosed, other than to those directly involved in the execution or ethical review of the study, without written authorization from Spero Therapeutics. It is, however, permissible to provide information to a volunteer in order to obtain consent.

SIGNATURE PAGE

Protocol Title: A Phase 3, randomized, double-blind, double-dummy, multicenter, multinational study to assess the efficacy and safety of orally administered tebipenem pivoxil hydrobromide (TBP-PI-HBr) compared to intravenously administered imipenem-cilastatin in patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP)

The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol. The undersigned agree that the trial will be carried out in accordance with the clinical study protocol, Good Clinical Practice, with the Declaration of Helsinki (with amendments), and with the laws and regulations of the countries in which the study takes place.

Any modifications of the clinical study protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Sponsor Approval:

The protocol has been approved by Spero Therapeutics, Inc.

Responsible Medical Officer:

Signature: Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 26-Aug-2024 | 1:57:36 PM EDT [redacted] Date: 26-Aug-2024

Name (print): [redacted], MD

Title: [redacted]

INVESTIGATORS ACKNOWLEDGEMENT

I have read the PIVOT-PO protocol, Study SPR994-305, a Phase 3, randomized, double-blind, double-dummy, multicenter, multinational study to assess the efficacy and safety of orally administered tebipenem pivoxil hydrobromide (TBP-PI-HBr) compared to intravenously (IV) administered imipenem-cilastatin in patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP).

I have fully discussed the objective(s) of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and not to be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a patient in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) Guidance (FDA 2018a), European Union (EU) Clinical Trials (CT) Regulation 536/2014 (European Commission 2014), and with the applicable Regulatory Authority (RA) requirements.

I understand that failure to comply with the requirements of the protocol may lead to my termination as an Investigator for this study.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time, or for any reason, communication of such a decision may be in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

Principal Investigator (PI) Name:	
Site Name:	
Site Number:	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a Serious Adverse Event (SAE), the Investigator must e-mail or fax the Clinical Trial SAE Form within 24 hours to Parexel:

- **E-mail**: sperosafety@parexel.com
- **Pharmacovigilance SAE Fax Number:** 1-781-434-5957
- **For protocol- or safety-related issues during normal business hours, the Investigator must contact the PSI CRO Medical Monitor.**

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product (IP) quality complaints to Spero Therapeutics, Inc. or its representative within one business day. This includes any instances wherein the quality or performance of a Spero Therapeutics, Inc. product (marketed or investigational) does not meet expectations (e.g., inadequate, or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (e.g., wrong product such that the label and contents are different products).

Please see the pharmacy manual for product quality complaint contact information.

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1. SYNOPSIS

Study Title:	A Phase 3, randomized, double-blind, double-dummy, multicenter, multinational study to assess the efficacy and safety of orally administered tebipenem pivoxil hydrobromide (TBP-PI-HBr) compared to intravenously administered imipenem-cilastatin in patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP)
Study Number:	SPR994-305
Phase of Development:	3
Version/Date:	26Aug2024; Version 4.1
Investigational Product:	Tebipenem pivoxil hydrobromide (TBP-PI-HBr; previously known as SPR994)
Comparator Product:	Imipenem-cilastatin
Investigational and Comparator Product Dose, and Mode of Administration:	Treatment Group 1: TBP-PI-HBr 600 mg (2×300 mg film-coated immediate-release tablets), administered orally (PO) every 6 hours (q6h ±1 hour [h]) plus dummy infusion (0.9% sodium chloride) administered intravenously (IV) over 30 minutes (min) q6h (±1 h) Treatment Group 2: Imipenem-cilastatin, 500 mg administered IV over 30 min q6h (±1 h) plus matched dummy tablets administered PO q6h (±1 h) The total duration of study treatment will be 7-10 days.
Study Population:	Male and female patients aged 18 years or older, hospitalized for the treatment of cUTI or AP
Planned Sample Size:	The study is planned to enroll approximately 2648 patients (1324 per treatment group) to achieve a target sample size of approximately 1588 patients (794 per treatment group) for the primary analysis population (Microbiological Intent-to-Treat [micro-ITT] Population). The final number of randomized patients may vary based on the evaluability rate for the micro-ITT Population. The target sample size assumes a 60% evaluability rate for the micro-ITT Population. Response rates of 60% and 58% are assumed for IV imipenem-cilastatin and oral TBP-PI-HBr, respectively. The proposed sample size will yield approximately 1588 evaluable patients (794 per treatment group) for the primary analysis, which will provide 89% power with a 1-sided significance level of 0.025 for the assessment of non-inferiority (NI) of oral TBP-PI-HBr to IV imipenem-cilastatin with a -10% margin. An unblinded interim analysis (IA) to assess both efficacy and futility will be performed by an unblinded Independent Data Monitoring Committee (IDMC) when 60% of the patients in the micro-ITT Population (approximately 954 patients) have achieved the TOC visit, potentially allowing for early termination of the study based on certain pre-specified criteria. The study will utilize a group sequential design with one planned IA using error spending boundaries. Refer to Section 10.1 for additional details.

Number of Clinical Centers:	Approximately 160 clinical centers
Primary Objective	To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to the overall response (combined clinical cure plus microbiological eradication) at the Test-of-Cure (TOC) visit in hospitalized adult patients (≥18 years of age) with cUTI/AP. A description of the primary estimand and estimand rationale is presented in Section 3.1.
Secondary Objectives:	• To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall response rates at the TOC visit in patients with cUTI/AP in the Microbiologically Evaluable (ME) Population. • To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall response rates at End-of-Treatment (EOT) and Late Follow-up (LFU) visits in patients with cUTI/AP. • To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to clinical response rates at EOT, TOC, and LFU visits in patients with cUTI/AP. • To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to microbiological response rates at EOT, TOC, and LFU visits in patients with cUTI/AP. • To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall, clinical and microbiological response rates at TOC, EOT and LFU visits among cUTI/AP patients infected with drug-resistant Enterobacterales uropathogens, e.g., extended spectrum β-lactamase (ESBL)-producing, fluoroquinolone-nonsusceptible (FQ-NS), and/or trimethoprim-sulfamethoxazole-resistant (TMP-SMX-R) strains. • To assess the safety and tolerability of oral TBP-PI-HBr as compared to IV imipenem-cilastatin in patients with cUTI/AP. • To provide tebipenem (TBP) plasma concentration data to characterize the pharmacokinetics (PK) of TBP in the target population using PK modelling. A description of the secondary estimands and estimands rationale is presented in Section 3.1.2.
[redacted]	[redacted]

	[redacted]
Permitted/Prohibited Adjunctive Antimicrobial Therapy:	Concomitant administration of non-study, potentially effective, systemic antimicrobial therapy that would potentially confound the assessment of treatment outcomes is not allowed, except in cases of cUTI/AP study treatment clinical failure. Topical antimicrobials and antimicrobials for the treatment of *Clostridioides difficile* infection are permitted. For treatment of new and unexpected infections other than cUTI/AP (i.e., adverse events [AEs]), narrow spectrum antimicrobials which are not expected to have potential to treat the causative pathogen(s) should be selected whenever possible.
Study Design/Methods:	This is a Phase 3, randomized double-blind, double-dummy, multicenter, multinational prospective study to assess the efficacy and safety of TBP- PI- HBr compared to IV imipenem-cilastatin in patients with cUTI/AP. Eligible patients with a clinical diagnosis of cUTI/AP suitable to start empiric IV antimicrobials, who can tolerate oral medication will be randomized in a 1:1 ratio to receive either oral TBP-PI-HBr (600 mg PO q6h) or IV imipenem-cilastatin (500 mg IV q6h) with matched dummy oral or IV administration. Randomization will be stratified by age at time of consent (≥18 to <65 years vs. ≥65 years), baseline diagnosis (cUTI vs. AP), and presence or absence of urinary tract instrumentation at Baseline. Patients who meet the disease definition of cUTI (e.g., underlying functional or anatomical urinary tract abnormality; per Inclusion Criterion 4.a) and have additional clinical evidence of AP (e.g., flank pain or costovertebral angle tenderness; per Inclusion Criterion 4.b) should be randomized as cUTI. At least 30% of patients will be randomized with a diagnosis of AP at study entry.
Rationale for Comparator:	Imipenem-cilastatin is a parenteral carbapenem antimicrobial approved for the treatment of cUTI/AP in many countries and is considered an empiric standard-of-care (SOC) treatment option for patients with serious bacterial infections, including cUTI/AP. Imipenem has a similar spectrum of in vitro and in vivo antimicrobial activity to TBP against common pathogens

	that cause cUTI/AP, including ESBL-producing Enterobacterales and certain Gram-positive uropathogens (e.g., *Enterococcus faecalis, Staphylococcus aureus, Staphylococcus saprophyticus*).
Study Duration:	The total duration of study participation will be approximately 28 days following the first dose of trial therapy. The total duration of study treatment (IV or oral) will be 7-10 calendar days. Study procedures will be completed at the following visits: • **Screening Visit,** Day -1 to 1: Screening procedures must be performed within 24 h prior to randomization on Day 1 to determine study eligibility. • **Treatment Visits:** Day 1 up to Day 10: Following initial urine and blood cultures, eligible patients will be randomized and receive IP(TBP-PI-HBr or imipenem-cilastatin) and matched dummy tablets or dummy infusions during this treatment period. Study treatment may start on the same calendar day as the Screening visit. • **End-of-Treatment (EOT) Visit** will be completed on the last day of study treatment administration (e.g., Day 7-10), or the following day (e.g., allowing a 1-day window to complete EOT procedures). Patients requiring more than 10 days of treatment will be discontinued from IP or comparator, assessed at EOT as clinical failure, and treated with an appropriate open-label antimicrobial at the discretion of the Investigator. The patient will remain in the study for the remaining visits. • **Test-of-Cure (TOC) Visit, Day 17** (±2 days) post randomization • **Late Follow-Up (LFU) Visit, Day 28** (±2 days) post randomization
Inclusion Criteria:	Patients meeting all the following inclusion criteria should be considered for randomization in the study: 1. male and female patients at least 18 years of age; patients enrolled in India must be ≤90 years of age 2. able to provide informed consent (for further details regarding patient consenting, refer to Section 11.3.1) 3. able to ingest oral tablets for the anticipated treatment duration. If present at Baseline, nausea and/or vomiting should be mild or well controlled with antiemetic therapy 4. have a diagnosis of cUTI or AP as defined below: **a. <u>cUTI definition:</u>** at least TWO of the following signs and symptoms: i. chills, rigors, or fever (oral, tympanic, rectal or core temperature >38.0°C [>100.4°F]); fever must be observed and documented by a health care provider ii. dysuria, urgency to void, or increased urinary frequency iii. nausea or vomiting, as reported by the patient iv. lower abdominal pain, suprapubic pain, pelvic pain, or flank pain/costovertebral angle tenderness

	AND at least **ONE** of the following risk factors for cUTI: i. implanted urinary tract instrumentation (e.g., nephrostomy tube, ureteric stents, or other urinary tract prosthetic material), ongoing intermittent bladder catheterization, or presence of an indwelling bladder catheter (Note: bladder catheters that have been in place for >24 h prior to Screening must be removed or replaced prior to collection of the Screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated) ii. current known functional or anatomical abnormality of the urogenital tract, including anatomic abnormalities of the urinary tract, neurogenic bladder, or post-void residual urine volume of ≥100 milliliters (mL) within the past 6 months iii. complete or partial obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis, urethral stricture) that is expected to be medically or surgically treated during study drug therapy (prior to EOT visit) iv. known intrinsic renal disease with blood urea nitrogen (BUN) >20 mg/deciliter (dL), or blood urea >42.8 mg/dL, or serum creatinine (Cr) >1.4 mg/dL v. urinary retention, including urinary retention in men due to previously diagnosed benign prostatic hyperplasia (BPH). **b. <u>AP definition:</u>** acute flank pain (onset within 7 days prior to randomization) or costovertebral angle tenderness on physical examination **AND** at least **ONE** of the following signs and symptoms: i. chills, rigors, or fever (oral, tympanic, rectal or core temperature >38.0°C [>100.4°F]); fever must be observed and documented by a health care provider ii. peripheral white blood cell count (WBC) >10,000/cubic millimeter (mm^3) or bandemia (>15% immature polymorphonuclear neutrophils [PMNs], regardless of WBC count) iii. nausea or vomiting, as reported by the patient iv. dysuria, urgency to void, or increased urinary frequency. *Note*: Patients who meet the definition for cUTI (refer to Inclusion Criterion a) and have flank pain or costovertebral tenderness should be randomized as cUTI rather than AP. 5. have an adequate urine specimen for evaluation and culture obtained within 24 h prior to randomization with evidence of pyuria that includes at least one of the following: a. at least 10 WBCs per high power field (HPF) in urine sediment b. at least 10 WBCs per mm^3 in unspun urine c. positive leukocyte esterase (LE) on urinalysis.

	Note: Patients may be randomized and administered study drug prior to knowledge of urine culture results, but pyuria must be documented. 6. expectation, in the judgment of the Investigator, that the patient will survive with effective antimicrobial therapy and appropriate supportive care for the anticipated duration of the study 7. willing to comply with all the study activities and procedures throughout the duration of the study 8. willing to agree to use a highly effective method of birth control; male patients must agree to not engage in sexual activity with a female partner that could lead to pregnancy (i.e., heterosexual vaginal intercourse) or must agree to use an effective barrier method of contraception from Screening through the LFU visit and for 90 days following the last dose; females of childbearing potential (FOCP) must have a negative pregnancy test at Screening and agree to abstain from sexual activity that could lead to pregnancy (i.e., heterosexual vaginal intercourse or in vitro fertilization) from the time of Screening through the EOT visit, or agree to use a highly effective method of contraception from the time of Screening throughout the study (through the LFU visit). Highly effective methods of birth control include one or more of the following: a. an approved hormonal contraceptive associated with inhibition of ovulation including oral, implantable, transdermal, injectable, intravaginal contraceptive used consistently for at least 1 month prior to study drug dosing b. an intrauterine device or intrauterine hormone-releasing system c. male sexual partner who has been vasectomized for at least 3 months prior to Screening and who has obtained a follow-up negative sperm count. 9. female of nonchildbearing potential based on at least 1 of the following criteria: a. post-menopausal status defined as amenorrhea for at least 12 months prior to randomization b. Follicle Stimulating Hormone (FSH) levels in the laboratory defined post-menopausal range; in the absence of amenorrhea for at least 12 months prior to randomization, at least two FSH measurements demonstrating levels in the post-menopausal range are required c. patient report of surgical sterilization (i.e., bilateral tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy) at least 6 weeks prior to randomization.

Exclusion Criteria:	Patients meeting any of the following exclusion criteria will not be enrolled in the study: 1. presence of any known or suspected disease or condition that may confound the assessment of efficacy, including but not limited to the following: a. perinephric or renal corticomedullary abscess b. uncomplicated urinary tract infection (uUTI [acute cystitis that does not meet the cUTI disease definition; refer to Inclusion Criterion 4.a]) c. polycystic kidney disease d. recent history of trauma to the pelvis or urinary tract e. confirmed or suspected acute or chronic bacterial prostatitis, orchitis, or epididymitis f. chronic vesicoureteral reflux g. previous or planned renal transplantation h. previous or planned cystectomy or ileal loop surgery i. known or suspected non-renal source of infection (e.g., infective endocarditis, osteomyelitis, meningitis, pneumonia) j. confirmed or suspected infection that is caused by a pathogen that is resistant to either study drug (e.g., carbapenem-resistant pathogen), including infection caused by fungi (e.g., candiduria) or mycobacteria (e.g., urogenital tuberculosis) or an intrinsically-resistant bacterial species not expected to respond to oral IP or comparator IV (e.g., *Pseudomonas* species). 2. gross hematuria requiring intervention other than administration of study drug or removal/placement of urinary tract instrumentation 3. urine Gram stain (if performed by site) fails to demonstrate a Gram-negative bacillus (*i.e., negative Gram stain or Gram stain demonstrating only a Gram-positive organism*) *Note*: Urine Gram stain should be performed, if possible, to inform eligibility but is not mandatory for Screening. 4. urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required for relieving an obstruction or placing urinary tract instrumentation) 5. creatinine clearance (CrCl) of ≤30 mL/min, as estimated by the Cockcroft-Gault formula: $\mathrm{eC_{Cr}}[\mathrm{mL/min}] = \frac{(140-\text{Age [yrs]})\times\text{Body Weight [kg]}\times[0.85 \text{ if Female}]}{72\times\text{Serum Creatinine [mg/dL]}}$ 6. anticipated concomitant use of non-study antimicrobial drug therapy between randomization and the LFU visit that would potentially effect outcome evaluations of cUTI/AP, including but not limited to antimicrobials with potential activity against Gram-negative pathogens, antimicrobial drug prophylaxis, and antimicrobial bladder irrigation

	7. receipt of a potentially effective antimicrobial within 72 h prior to study randomization 8. severe hepatic impairment at Screening, as evidenced by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5×upper limit of normal (ULN) or total bilirubin >3×ULN, or clinical signs of cirrhosis or end-stage hepatic disease (e.g., ascites, hepatic encephalopathy) 9. pregnant or lactating women 10. history of epilepsy or known seizure disorder (excluding a history of childhood febrile seizures) 11. history of proven or suspected *Clostridioides difficile* associated diarrhea 12. receipt of any investigational device or investigational medication during the last 30 days or 5 half-lives, whichever is longer, prior to randomization 13. known history of human immunodeficiency virus (HIV) infection with known CD4 count <200/mm^3 or acquired immunodeficiency syndrome (AIDS)-defining illness within the past year 14. presence of immunodeficiency or an immunocompromised condition including neutropenia (<1,000 neutrophils/mm^3 obtained from the local laboratory at Screening), hematologic malignancy, bone marrow transplant, or receiving immunosuppressive therapy such as cancer chemotherapy, medications for the rejection of transplantation, and long-term use of systemic corticosteroids (e.g., ≥20 mg/day of prednisone or systemic equivalent for at least 2 weeks) 15. QT interval corrected using Fridericia's formula (QTcF) >480 msec based on screening electrocardiogram (ECG) 16. history of significant hypersensitivity or allergic reaction to β-lactam antimicrobials (e.g., cephalosporins, penicillins, carbapenems), product excipients (mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, colloidal silicon dioxide, and Opadry®) or any contraindication to the use of imipenem-cilastatin 17. history of known genetic metabolism anomaly associated with carnitine deficiency (e.g., carnitine transporter defect, methylmalonic aciduria, propionic acidemia) 18. requirement for concomitant use of valproic acid, divalproex sodium, or probenecid between randomization and EOT 19. unable or unwilling to comply with the protocol 20. an employee of the Investigator or study center with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as a family member of the employee or the Investigator.

Efficacy Endpoints:	**Primary Endpoint:** • Overall response (combined per-patient clinical cure and favorable microbiological response) at the TOC visit in the micro-ITT Population, as defined by: a. clinical cure: complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted, and patient is alive b. favorable microbiological response (microbiological eradication): reduction of Baseline uropathogens to $<10^3$ CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline and patient is alive. **Secondary Endpoints**: • Overall response at the TOC visit in the ME Population • Overall response at the EOT and LFU visits in the micro-ITT and ME Populations • Clinical response at the EOT, TOC and LFU visits in the micro-ITT, Clinically Evaluable (CE) and ME Populations • Microbiological response at the EOT, TOC and LFU visits in the micro-ITT and ME Populations • Overall, Clinical and Microbiological response at the TOC, EOT and LFU visits in the micro-ITT and ME Populations in patients with drug-resistant Enterobacterales • Treatment-emergent AEs (TEAEs) and serious AEs (SAEs) and change from Baseline results for clinical laboratory tests, ECGs, and vital sign measurements in the Safety Population • TBP plasma concentration in the TBP PK Population [redacted]
Safety Endpoints and Assessments:	Safety and tolerability up to the LFU visit in the Safety Population based on TEAEs, clinical laboratory (hematology, clinical chemistry, and urinalysis) changes from Baseline, ECGs, and vital sign changes in the Safety Population

Microbiological Assessments:	Urine specimens for culture and Gram stain (where applicable) will be obtained at the Screening/Baseline, [redacted] EOT, TOC, and LFU visits and, in addition, as clinically indicated throughout the study. At Screening, two sets of blood cultures (i.e., one aerobic blood culture bottle and one anaerobic (if possible) blood culture bottle from two separate venipuncture sites for a total of four bottles) should be collected. Blood cultures should be repeated as necessary until negative blood cultures are obtained.
Pharmacokinetic Assessments:	Intensive blood sampling for plasma PK assessment will be performed in a subset of patients (at selected sites; approximately 40 patients, 20 per treatment group 7 samples/patient) following any oral dose on Day 2 or Day 3 (fifth, sixth, seventh, or eighth dose) according to the schedule outlined in Appendix 2. Intensive PK assessment is optional, patients will need to sign a separate consent. Sparse PK sampling will be performed for all other patients (3 samples/patient) following any oral dose on Day 2 or Day 3 (fifth, sixth, seventh, or eighth dose). TBP plasma concentration-time data from TBP-PI-HBr-treated patients (Treatment Group 1) will inform a population PK model to be used for estimation of individual PK profiles, to be separately reported. [redacted] in the subset of patients participating in intensive blood sampling for plasma PK (approximately 40 patients, 20 per treatment group) as outlined in Appendix 2.
Statistical Considerations:	**Analysis Populations**: • **Intent-to-Treat (ITT) Population**: All patients who were randomized, regardless of whether they received any IP or comparator. Patients will be summarized by the treatment to which they were randomized. • **Safety Population**: Randomized patients who received any amount of IP or comparator. Patients will be summarized by the treatment which they received. • **Microbiological Intent-to-Treat (micro-ITT) Population**: All randomized patients who have all of the following: o A baseline urine culture demonstrating $\geq 10^5$ CFU/mL of an Enterobacterales uropathogen (or the same Enterobacterales pathogen is present concurrently in blood cultures and in urine) against which imipenem has antibacterial activity o No additional pathogens other than an additional Enterobacterales species, *Enterococcus faecalis, Staphylococcus aureus, or Staphylococcus saprophyticus* are identified in the baseline urine culture at $\geq 10^5$ CFU/mL (or the same pathogen is present concurrently in blood cultures and in urine). In addition, where

	E.faecalis, S. aureus, *or S. saprophyticus* are identified, imipenem must have antibacterial activity. ○ No more than 2 microorganisms identified in the baseline urine culture, regardless of colony count *Note*: For Enterobacterales, antimicrobial activity for imipenem is defined as Susceptible according to CLSI Criteria (MIC ≤1 µg/mL); CLSI 2023. For *E. faecalis,* antimicrobial activity will be presumed where the ampicillin MIC is ≤8 µg/mL. For *S. aureus,* antimicrobial activity will be presumed where the oxacillin MIC is ≤2 µg/mL. For *S. saprophyticus,* antimicrobial activity will be presumed where the oxacillin MIC is ≤0.5 µg/mL. • **Clinically Evaluable (CE) Population**: Patients who meet the definition for the ITT Population, have no important protocol deviations that would affect the assessment of efficacy including, but not limited to, a minimum duration of study treatment and treatment compliance ≥80% of expected number of doses (additional deviations as further defined in the Statistical Analysis Plan [SAP]), and had an outcome assessed as clinical cure or clinical failure at EOT, TOC, and/or LFU visits, respectively. • **Microbiologically Evaluable (ME) Population**: Patients who meet the definitions of both the micro-ITT Population and CE Population. In addition, to be included in the ME Population, patients must not have a microbiological outcome of indeterminate. *Note*: The ME and CE Populations will be defined for each respective visit (e.g., ME-EOT, ME-TOC, and ME-LFU). • **PK Population**: All patients treated with at least one relevant dose of TBP-PI-HBr with at least one quantifiable plasma or [redacted] sample according to the subpopulations outlined below: ○ **Intensive Plasma PK Subgroup:** approximately 20 TBP-PI-HBr-treated patients with at least one quantifiable plasma PK sample ○ **Sparse Plasma PK Subgroup:** all remaining TBP-PI-HBr-treated patients with at least one quantifiable plasma PK sample ○ [redacted]. • **Gram-positive Population:** All patients in the ITT population with a baseline urine culture demonstrating ≥10^5 CFU/mL of *E. faecalis, S. aureus,* and/or *S. saprophyticus* (or the same pathogen is present concurrently in blood cultures and in urine) against which imipenem has antibacterial activity AND no more than 2 microorganisms are identified in the urine culture regardless of colony count. Additionally, if a patient has more than 1 pathogen identified, the second pathogen

	must be *E. faecalis, S. aureus, S. saprophyticus*, or an Enterobacterales spp. This population will be used for supplemental analysis of the treatment effect for these Gram-positive pathogens and will be described in the SAP. **Statistical Analysis:** The primary analysis will be the comparison of the overall response at the TOC visit for patients in the micro-ITT Population. The testing procedure at the IA and the final analysis will compare the NI test statistics with the stopping boundaries. Test statistics of the response rate difference between the two treatment groups for NI (using -10% margin for oral TBP-PI-HBr minus IV imipenem-cilastatin) will be calculated using the Miettinen and Nurminen method stratified by age category (≥18 to <65 and ≥65 years), baseline diagnosis (AP or cUTI), and presence or absence of urinary tract instrumentation at Baseline and compared to the stopping boundaries. If NI is established, test statistics of the success rate difference between the two treatment groups for superiority will be calculated using the same method to compare with the stopping boundary for superiority. Details on the testing procedure and stopping boundaries are provided in the IDMC analysis plan. For details about handling of missing data refer to Section 10.8.2. Secondary efficacy endpoints for clinical response and microbiological response will not include formal hypothesis testing or adjustments for multiplicity. Safety data will be summarized using descriptive statistics for the Safety Population.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AP	acute pyelonephritis
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma drug concentration-time curve
AUC_{0-24}	area under the plasma drug concentration time curve from time 0 to 24 hours
β-HCG	serum beta human chorionic gonadotropin
Beta-lactamases	β-lactamases
BP	blood pressure
BPH	benign prostatic hyperplasia
BUN	blood urea nitrogen
CE	Clinically Evaluable
CFU	colony forming unit
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum observed concentration
Cr	creatinine
CrCl	creatinine clearance
CRF	case report form
CRO	Contract Research Organization
CS	clinically significant
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
cUTI	complicated urinary tract infection
eCRF	electronic case report form
EC	Ethics Committee
ECG	electrocardiogram
EMA	European Medicines Agency

Abbreviation	Definition
EOT	End-of-Treatment
ESBL	extended spectrum β-lactamase
EU	European Union
f	free drug
FDA	Food and Drug Administration
FQs	fluoroquinolones
FQ-NS	fluoroquinolone-nonsusceptible
FOCP	female of childbearing potential
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GI	gastrointestinal
h	hour
Hb	hemoglobin
HCG	human chorionic gonadotropin
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPF	high power field
IA	interim analysis
IB	Investigational Brochure
ICE	intercurrent events
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	intravenous(ly)
LC/MS/MS	liquid chromatography tandem mass spectrometry
LE	leukocyte esterase

Abbreviation	Definition
LFU	Late Follow-Up
MDR	multidrug-resistant
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
micro-ITT	Microbiological Intent-to-Treat
min	minutes
MRSA	methicillin-resistant *Staphylococcus aureus*
NI	non-inferiority
NOAEL	no observed adverse effect level
OTC	over-the-counter
P	pulse
PD	Pharmacodynamic(s)
PI	Principal Investigator
PK	pharmacokinetic(s)
PMN	polymorphonuclear neutrophils
PO	orally
QTcF	Fridericia's formula
qXh	every X hours
QD	once daily
RA	Regulatory Authority
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOA	Schedule of Assessments
SOC	Standard-of-Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
λz	terminal disposition rate constant/terminal rate constant
TBP	tebipenem
TBP-PI	tebipenem pivoxil

Abbreviation	Definition
TBP-PI-HBr	tebipenem pivoxil hydrobromide
TEAE	treatment-emergent adverse event
T	temperature
TOC	Test-of-Cure
TMP-SMX	trimethoprim-sulfamethoxazole
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
UTI	urinary tract infection
uUTI	uncomplicated urinary tract infection
WBC	white blood cell
WHO	World Health Organization

2. INTRODUCTION

2.1. Background and Rationale for the Study

Urinary tract infection (UTI) is one of the most common bacterial infections in adults in both the community and hospital setting. Complicated UTI (cUTI) is a subset of UTIs in which the infection has extended beyond the bladder, frequently associated with functional or anatomic urinary tract abnormalities; acute pyelonephritis (AP), infection of the renal parenchyma, can occur in patients with or without functional or anatomic abnormalities of the urinary tract. Gram-negative bacteria of the Enterobacterales order (e.g., *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and *Proteus* spp.) are the predominant pathogens causing cUTI and AP, although Gram-positive bacteria e.g., *Enterococcus* spp., *Staphylococcus aureus* and coagulase negative staphylococci are also implicated.

Oral antibiotics including cephalosporins, fluoroquinolones (FQs), and trimethoprim-sulfamethoxazole (TMP-SMX) have been widely used for treating cUTI/AP in the outpatient setting. However, the management of cUTI/AP is increasingly complicated by the rising prevalence of bacterial resistance to existing oral agents, predominantly due to β-lactamase-producing uropathogens (e.g., Enterobacterales pathogens producing extended spectrum β-lactamases [ESBLs] or AmpC, β-lactamases) (Critchley 2019). These resistant strains are often co-resistant to other standard-of-care (SOC) oral antibiotics, including the FQs and TMP-SMX. Among US patients hospitalized with UTI, the incidence of ESBL-producing and FQ-resistant Enterobacterales are 20% and 33%, respectively – exceeding guideline thresholds for avoiding empiric use of existing oral agents (Talan 2021). The increasing prevalence of multi-drug resistant (MDR) Gram-negative pathogens causing serious bacterial infections such as cUTI/AP has been associated with increased morbidity, mortality, and greater costs of care and represents a serious global threat to public health (Carreno 2020, CDC 2019, Lancet 2022, Zilberberg 2021). Despite this increase, resistance to carbapenems remains low (<2%) (Critchley 2019, Talan 2021, CDC 2019).

In the setting of resistance to other classes of antibiotics and lack of alternative oral options, patients with cUTI/AP are commonly hospitalized to receive intravenous (IV) antibiotic therapy, most commonly with a carbapenem antibiotic (e.g., ertapenem, imipenem and meropenem) which have demonstrated efficacy in complicated bacterial infections, including cUTI/AP, and remain active against most MDR Gram-negative uropathogens due to their inherent stability against most ESBL and Class C beta-lactamases (β-lactamases).

There is an urgent need for new oral options for the treatment of cUTI/AP, including those infections caused by MDR Gram-negative uropathogens. No oral carbapenem options currently exist for patients with cUTI/AP who would be otherwise appropriate for oral therapy. Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is being developed as an oral carbapenem alternative to IV carbapenems with broad-spectrum activity against common uropathogens. A new effective oral cUTI/AP treatment option would potentially limit the need for hospitalization and/or venous catheterization for patients otherwise appropriate for oral therapy, thereby reducing risk of treatment associated complications and nosocomial infections and ultimately decreasing costs of care.

This Phase 3 study is designed to assess the safety, tolerability, and effectiveness of TBP-PI-HBr as compared with a SOC IV carbapenem, imipenem-cilastatin in the treatment of patients with cUTI/AP. A previous Phase 3 Study of TBP-PI-HBr versus IV ertapenem (ADAPT-PO) provided preliminary safety and efficacy data for TBP-PI-HBr in the treatment of patients with cUTI/AP (Eckburg 2022; refer to Section 2.2.3). The current study is designed to provide confirmatory evidence of the safety and efficacy of TBP-PI-HBr versus an alternate IV carbapenem comparator.

2.2. Tebipenem-Pivoxil-Hydrobromide (TBP-PI-HBr)

TBP-PI-HBr is an oral prodrug of tebipenem (TBP, the active moiety), a broad-spectrum carbapenem antimicrobial from the β-lactam class of antibiotics with demonstrated in vitro and in vivo activity against both Gram-negative and Gram-positive bacteria.

Tebipenem pivoxil (TBP-PI) is a related pivaloyloxymethyl prodrug formulation of TBP which allows for oral absorption and improved bioavailability of TBP. TBP-PI is currently approved and marketed only in Japan as a pediatric oral granule formulation for the treatment of otitis media, sinusitis, and pneumonia in children (Orapenem® Fine Granules 10%; Meiji Seika Pharma Co., Ltd, "Meiji").

TBP-PI-HBr is the HBr salt form of TBP-PI, which has improved drug product properties that enable a high dosage strength tablet formulation relative to those of Orapenem. Both TBP-PI-HBr and TBP-PI are prodrugs that rapidly convert to the same active moiety, TBP, in enterocytes of the gastrointestinal (GI) tract by intestinal esterases (Kato 2010). Accordingly, nonclinical data for TBP and/or TBP-PI provide supportive data for TBP-PI-HBr.

Of note, tebipenem pivoxil hydrobromide, tebipenem pivoxil, and tebipenem have been abbreviated as TBP-PI-HBr, TBP-PI, and TBP, respectively, in this document but may appear as TBPM-PI-HBr, TBPM-PI, and TBPM, respectively, in earlier protocols, data in the TBP- PI-HBr Investigator's Brochure (IB), and/or published data relevant to tebipenem. TBPM has been adapted to TBP in recent documents to align with the Clinical and Laboratory Standards Institute (CLSI) abbreviation for tebipenem (CLSI 2023).

2.2.1. Nonclinical Information

Comprehensive nonclinical safety pharmacology, pharmacokinetics (PK) and microbiology studies have been conducted with TBP, TBP-PI and TBP-PI-HBr. Please refer to the current TBP-PI-HBr IB for detailed summaries of preclinical data.

2.2.2. Microbiologic Activity

TBP, the pharmacologically active moiety of TBP-PI-HBr, has demonstrated broad-spectrum activity against clinically important Gram-positive and Gram-negative pathogens causing cUTI/AP, including MDR organisms, e.g., ESBL and AmpC β-lactamase-producing Enterobacterales, including strains co-resistant to FQs and/or TMP-SMX.

TBP activity against common Enterobacterales bacteria is consistent with that of currently available IV carbapenems such as imipenem and meropenem. Among 1717 clinical Enterobacterales isolates collected from patients with UTIs in the 2019 US surveillance, TBP

drug concentration that inhibits the growth of 90% of test organisms (MIC_{90}) value was 0.06 µg/mL compared with MIC_{90} values of 1.0 and 0.06 µg/mL for imipenem and meropenem, respectively. Specifically, among *E. coli,* the most frequently encountered uropathogen, the MIC_{90} value for TBP was 0.015 µg/mL. TBP was active against prevalent ESBL-producing and Class C β-lactamase-producing Enterobacterales isolates. All phenotypic ESBL-producing, meropenem-susceptible, levofloxacin non-susceptible and/or TMP-SMX-R *E. coli* isolates were inhibited by TBP at concentrations ≤0.5 µg/mL.

The broad-spectrum activity of TBP against β-lactamase-producing organisms was confirmed against an extensive collection of isogenic strains of *E. coli* expressing narrow spectrum β-lactamases (TEM, SHV), ESBLs such as CTX-M-15, and Class C β-lactamase-producing organisms. The stability of TBP to hydrolysis by these enzymes has also been established in biochemical studies. TBP, like the other carbapenems, was not active against organisms producing carbapenemases such as *K. pneumoniae* carbapenemase, OXA-48, NDM, and VIM β-lactamase.

TBP-PI-HBr does not have clinically significant (CS) activity against nonfermenting Gram-negative pathogens including *Pseudomonas aeruginosa, Stenotrophomonas maltophilia*, and *Acinetobacter* spp.*)* which are therefore not considered to be target pathogens for TBP-PI-HBr. As such, patients with confirmed or suspected cUTI/AP caused by nonfermenting Gram-negative bacilli are excluded from the study.

2.2.3. Clinical Information

The TBP-PI-HBr safety and PK profile has been well-characterized in eight Phase 1 clinical pharmacology studies enrolling healthy volunteers and patients with renal impairment as well as a recently completed Phase 3 comparative study (ADAPT-PO) in patients with cUTI/AP. Across all clinical studies to date, a total of 944 patients have received TBP-PI-HBr, including 896 patients receiving the planned dose (600 mg) or higher in single or repeat dose administrations.

Please refer to the current TBP-PI-HBr IB for detailed summaries of clinical PK, safety, and efficacy data.

Following oral administration of TBP-PI-HBr in both fasted and fed states, there is a generally linear relationship between dose and TBP exposure with no accumulation of TBP following dosing.

The effect of renal impairment on the PK of TBP is well-characterized in patients with various degrees of renal function and in patients with cUTI/AP. Similar to other β-lactam agents, TBP is predominantly renally cleared. The relationship between renal clearance and calculated creatinine clearance (CrCl) was found to be linear. Dose adjustment is recommended for TBP-PI-HBr in patients with CrCl <50 mL/minute (min) (refer to Section 6.2.1). Patients with severe renal impairment and end-stage renal disease (CrCl≤30 mL/min) are excluded from the study due to labeled precautions (for imipenem-cilastatin noting an increased potential for seizure activity in patients with CrCl ≤30 mL/min (PRIMAXIN® I.V. United States Package Insert [USPI]; PRIMAXIN® I.V. Summary of Product Characteristics [SmPC]).

No dose adjustments are required in adult patients with cUTI/AP based on age, weight, BMI, sex, or race/ethnicity as none of these covariates were associated with substantial differences in

TBP exposure in patients with cUTI/AP. Based on in vitro studies and in vivo studies, the potential for drug-drug interactions with TBP-PI-HBr is low. TBP-PI-HBr may be administered without respect to meals. Two prior Phase 1 studies demonstrated non-clinically meaningful differences in the absorption or TBP systemic exposure when oral TBP-PI-HBr was administered in a fasting or fed state.

Clinical data supporting the safety and preliminary efficacy of oral TBP-PI-HBr in patients with cUTI/AP are provided by a completed Phase 3, global, randomized, double-blind, double-dummy, comparative study of oral TBP-PI-HBr versus IV ertapenem in 1372 hospitalized adult patients with cUTI/AP (ADAPT-PO) (Eckburg 2022). Patients from Europe, South Africa, and the United States (US) were randomly assigned 1:1 to receive oral TBP-PI-HBr (600 mg administered every 8 hours [h]) or IV ertapenem (1 g administered every 24 h) for a duration of 7-10 days (up to 14 days in patients with bacteremia). Across all visits, clinical response rates were high in both treatment groups (>97% at End-of-Treatment [EOT], >93% at Test-of-Cure [TOC], and >88% at Late Follow-Up [LFU]), with the majority of microbiological failures at each visit being asymptomatic patients with recurrent bacteriuria. Secondary and subgroup analyses were consistent with the primary analysis.

Oral TBP-PI-HBr was well-tolerated in patients with cUTI/AP in the completed Phase 3 study and had a comparable safety profile to that of IV ertapenem. The overall incidence of adverse events (AEs) was approximately 26% in both treatment groups. The most commonly reported AEs were consistent with carbapenem class effects and/or expected changes for patients with cUTI/AP (Eckburg 2022, Vardakas 2018). Diarrhea, headache, and nausea were the only AEs reported in >1% of patients from either treatment group. Most AEs were mild or moderate in severity and non-treatment-limiting.

2.3. Benefit/Risk Assessment

Patients participating in this study will have a diagnosis of cUTI/AP with sufficient severity to warrant hospitalization and treatment with IV antimicrobials. Potential benefits to patients enrolled in the study include receipt of potentially effective antimicrobial therapy and medical management treatment for their infection. Consistent with the established unmet need for new oral therapies for the treatment of cUTI/AP, there is an overall potential benefit of the study to confirm the efficacy of a new effective carbapenem antimicrobial agent.

Potential risks include the possibility that TBP-PI-HBr will not be as effective as the comparator treatment, however this risk is mitigated by the study design which allows for the close monitoring of patients and option for change in therapy by the treating investigator.

The identified risks of TBP-PI-HBr to date suggest minimal safety or toxicity risks associated with TBP-PI-HBr which are considered consistent with that of IV carbapenems and will be well-monitored based on the study procedures. Detailed risk information is provided in the IB.

Imipenem-cilastatin is approved for the treatment of patients with cUTI and identified potential risks associated with imipenem-cilastatin are outlined in the product labeling (PRIMAXIN® I.V. USPI; PRIMAXIN® I.V. SmPC).

3. STUDY OBJECTIVES AND ESTIMANDS/ENDPOINTS

3.1. Objectives and Endpoints

The study objectives and endpoints are outlined in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to the overall response (combined clinical cure plus microbiological eradication) at the TOC visit in hospitalized adult patients (≥18 years of age) with cUTI/AP	Overall response (combined per-patient clinical cure and favorable microbiological response) at the TOC visit in the micro-ITT Population, as defined by: a. clinical cure: complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted, and patient is alive b. favorable microbiological response (microbiological eradication): reduction of Baseline uropathogens to $<10^3$ CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline and patient is alive
Secondary	
1. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall response rates at the TOC visit in patients with cUTI/AP in the ME Population	1. Overall response at the TOC visit in the ME Population
2. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall response rates at EOT and LFU visits in patients with cUTI/AP	2. Overall response at the EOT and LFU visits in the micro-ITT and ME Populations
3. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to clinical response rates at EOT, TOC, LFU visits in patients with cUTI/AP	3. Clinical response at the EOT, TOC and LFU visits in the micro-ITT, Clinically Evaluable (CE) and ME Populations
4. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to microbiological response rates at EOT, TOC, and LFU visits in patients with cUTI/AP	4. Microbiological response at the EOT, TOC and LFU visits in the micro-ITT and ME Populations
5. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall, clinical and microbiological response rates at TOC, EOT and LFU visits among cUTI/AP patients infected with drug-resistant Enterobacterales uropathogens e.g., ESBL-producing, fluoroquinolone-	5. Overall, Clinical and Microbiological response at the TOC, EOT and LFU visits in the micro-ITT and ME Populations in patients with drug-resistant Enterobacterales

Objectives	Endpoints
nonsusceptible (FQ-NS), and/or trimethoprim-sulfamethoxazole-resistant (TMP-SMX-R) strains	
6. To assess the safety and tolerability of oral TBP-PI-HBr as compared to IV imipenem-cilastatin in patients with cUTI/AP	6. Treatment-emergent AEs (TEAEs) and SAEs and change from Baseline results for clinical laboratory tests, ECGs, and vital sign measurements in the Safety Population
7. To provide tebipenem (TBP) plasma concentration data to characterize the PK of TBP in the target population using PK modelling	7. TBP plasma concentration in the TBP PK Population
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

AE, adverse event; AP, acute pyelonephritis; cUTI, complicated urinary tract infection; [redacted]; IV, intravenous; ECGs, electrocardiograms; EOT, End-of-Treatment; ESBLs, extended spectrum β-lactamase; fluoroquinolone-nonsusceptible, FQ-NS; LFU, Late Follow-up; micro-ITT, Microbiological Intent-to-Treat; ME, Microbiologically Evaluable; PK, pharmacokinetic; SAE, serious adverse event; TBP, tebipenem; TBP-PI-HBr, tebipenem pivoxil hydrobromide; TEAE, treatment-emergent adverse event; TMP-SMX-R, trimethoprim-sulfamethoxazole-resistant; TOC, Test-of-Cure.

3.1.1. Primary Objective and Estimand

Primary Objective:

To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to the overall response (combined clinical cure plus microbiological eradication) at the TOC visit in hospitalized adult patients (≥18 years of age) with cUTI/AP.

Primary Estimand:

The primary clinical question of interest is: What is the treatment effect with respect to the overall response at the TOC visit following treatment with oral TBP-PI-HBr 600 mg q6h compared to IV imipenem-cilastatin 500 mg q6h, each administered over 7-10 days duration, in patients with cUTI or AP due to qualifying uropathogens, regardless of treatment discontinuation for any reason?

Receipt of non-study systemic antimicrobial therapy for treatment of the index infection (cUTI/AP) will impact the endpoint definition.

The primary estimand is described by the following attributes:

- Population: Patients with cUTI or AP included in the Microbiological Intent-to-Treat (micro-ITT) Population (refer to Section 10.3)
- Treatment Condition: TBP-PI-HBr 600 mg PO q6h versus imipenem-cilastatin 500 mg IV q6h, each administered for 7-10 days duration
- Variables: Overall response (combined per-patient clinical cure and favorable microbiological response) at the TOC visit
    - Clinical cure is defined as complete resolution or significant improvement of signs and symptoms of cUTI or AP present at Baseline and no new signs or symptoms requiring such that no further antimicrobial therapy is warranted, and patient is alive
    - Favorable microbiological response (microbiological eradication) is defined as a reduction of Baseline uropathogens to $<10^3$ CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline and patient is alive
- Summary Measure: Difference in the overall response rates between the TBP- PI-HBr and imipenem-cilastatin treatment groups
- Intercurrent Events (ICE):
    - Study treatment discontinuation due to any reason will be evaluated using a treatment policy strategy, e.g., evaluation of the treatment effect regardless of study treatment discontinuation, or noncompliance (missed doses)
    - Use of non-study, potentially effective systemic antimicrobials to treat the cUTI/AP infection prior to the TOC visit will be evaluated using a composite strategy as captured through the clinical outcome definition, with these events defined as overall failures

    If the patient experiences both of these ICE then a composite strategy (assigning overall response as a failure) will be used from the point that the relevant systemic antimicrobial was taken.

The rationale for the primary estimand includes:

Assessment of the treatment effect regardless of whether the full course of therapy (7-10 days of treatment) was received reflects how patients may be treated in clinical practice. Hence, a treatment policy strategy is appropriate for treatment withdrawal before completion of 7-10 days of treatment.

Use of non-study potentially effective systemic antimicrobials may confound the interpretation of the clinical response to treatment and/or the interpretation of microbiologic outcome based on bacterial culture results; thus, receipt of concurrent non-study potentially effective systemic antimicrobials for treatment of the index infection (cUTI/AP) will be considered as a clinical failure.

Use of non-study systemic antimicrobial agents for infections other than cUTI/AP should be restricted to agents without anticipated activity against the Baseline pathogen whenever possible. Therefore, a favorable overall response precludes the use of other potentially effective systemic antimicrobials with potential activity against the Baseline pathogen(s) when initiated for the treatment of the index infection (cUTI/AP).

3.1.2. Secondary Objectives and Estimand

Secondary Objectives:

- To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall response rates at the TOC visit in patients with cUTI/AP in the ME population
- To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall response rates at EOT and LFU visits in patients with cUTI/AP
- To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to clinical response rates at EOT, TOC, and LFU visits in patients with cUTI/AP
- To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to microbiological response rates at EOT, TOC, and LFU visits in patients with cUTI/AP
- To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to microbiological response rates at EOT, TOC, and LFU visits among cUTI/AP patients infected with drug-resistant Enterobacterales uropathogens, e.g., ESBL-producing, fluoroquinolone-nonsusceptible (FQ-NS), and/or trimethoprim-sulfamethoxazole-resistant (TMP-SMX-R) strains
- To assess the safety and tolerability of oral TBP-PI-HBr as compared to IV imipenem-cilastatin in patients with cUTI/AP
- To provide tebipenem (TBP) plasma concentration data to characterize the pharmacokinetics of TBP in the target population using PK modeling.

Secondary Estimands:

Efficacy:

The secondary clinical efficacy questions of interest are: What is the treatment effect (with respect to the overall, clinical, and microbiological endpoints) for oral TBP-PI 600 mg q6h compared to IV imipenem-cilastatin 500 mg q6h, each administered for 7-10 days in patients with cUTI or AP due to qualifying Baseline uropathogen(s)?

Receipt of non-study systemic antimicrobials impacts the endpoint outcome definitions (see above).

For each of the secondary endpoints the estimand will follow a similar approach to the estimand for the primary endpoint and will use the same general strategies for the ICEs.

The summary measure for the secondary endpoints is based on the difference between treatment groups (TBP-PI-HBr vs. imipenem-cilastatin) and these endpoints will be descriptively summarized (i.e., no direct inferential comparison between treatment groups will be made).

Safety:

The safety endpoint will use a treatment policy strategy of the ICEs of withdrawal from treatment as the safety will be assessed at all post-Baseline assessments irrespective of whether the participant completed the treatment or received non-study concomitant antimicrobial therapy.

PK:

The TBP plasma concentrations will be assessed to inform population PK modeling and will be separately reported. Refer to Appendix 1 for the components of estimand for the secondary endpoints.

4. STUDY DESIGN

4.1. Overview of Study Design and Procedures

This is a Phase 3, randomized double-blind, double-dummy, multicenter, multinational prospective study to assess the efficacy and safety of oral TBP-PI-HBr compared to IV imipenem-cilastatin for the treatment of patients with cUTI/AP.

Eligible patients with a clinical diagnosis of cUTI/AP and suitable to start empiric IV antimicrobials, and who are able to tolerate oral medication, will be randomized in a 1:1 ratio to receive either:

- TBP-PI-HBr 600 mg (2×300 mg film-coated immediate-release tablets), administered orally (PO) every 6 h (q6h ±1 h) plus dummy infusion (0.9% sodium chloride) administered intravenously (IV) over 30 min q6h (±1 h)
- Imipenem-cilastatin, 500 mg administered IV over 30 min q6h (±1 h) plus matched dummy tablets administered PO q6h (±1 h)

A dummy infusion of normal saline and dummy matching placebo tablets will be used to maintain the blind. For further treatment group details refer to Section 6.1.

Randomization will be stratified by age at time of consent (≥18 to <65 years vs. ≥65 years), baseline diagnosis (cUTI vs. AP), and presence or absence of urinary tract instrumentation at Baseline (refer to Section 4.5.1). For the purposes of stratification, Baseline Instrumentation should be considered present if the patient has a urinary tract instrument anytime from the beginning of Screening until Randomization.

Patients who meet the disease definition of cUTI (e.g., underlying functional or anatomical urinary tract abnormality; per Inclusion Criterion 4.a) and have additional clinical evidence of AP (e.g., flank pain or costovertebral angle tenderness; per Inclusion Criterion 4.b) should be randomized as cUTI. At least 30% of patients will be randomized with a diagnosis of AP at study entry.

The study plans to enroll approximately 2648 patients (1324 per treatment group) to achieve a target sample size of approximately 1588 evaluable patients (794 per treatment group) for the primary analysis population (micro-ITT Population) which would provide 89% power with a 1-sided significance level of 0.025 for assessment of NI of oral TBP-PI-HBr to IV imipenem-cilastatin (refer to Section 10.2). The final number of randomized patients will depend on a planned interim analysis (IA) to be performed when 60% of the patients in the micro-ITT Population (approximately 954 patients) have response data available at the TOC visit, potentially allowing for early termination of the study based on certain pre-specified criteria (refer to Section 10.1).

Receipt of potentially effective systemic antimicrobials with activity against the Baseline uropathogen within the 72-hour window prior to randomization could impact the assessment of efficacy. Patients who received potentially effective systemic antimicrobials within 72 h prior to randomization will be excluded.

Refer to Section 5.1 and Section 5.2 for study inclusion and exclusion criteria, respectively.

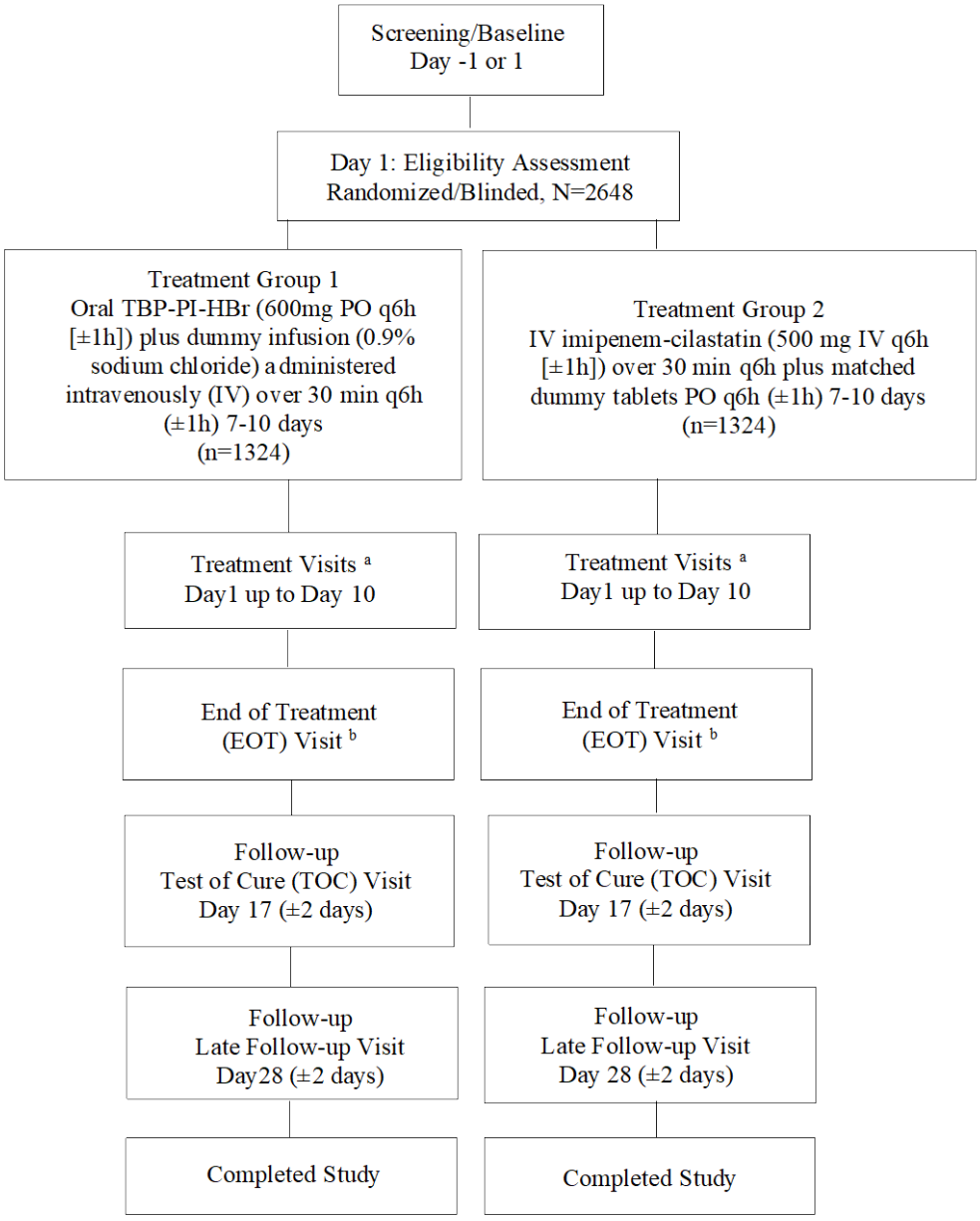
Refer to Section 7.1 for study visit details, and Section 7.2 for study outcome assessments and procedures detail.

The total duration of study participation will be approximately 28 days following the first dose of trial therapy. The total duration of study treatment (IV or oral) will be 7-10 calendar days. All patients will be treated for a minimum of 7 days (i.e., will be considered to have completed therapy after the last scheduled dose on study Day 7); however, treatment may continue for up to 10 days at the discretion of the Investigator. Patients will be hospitalized for the duration of their treatment.

Day 1 is the first day of IP or comparator administration. Patients who are prematurely discontinued from IP or comparator treatment should undergo all EOT visit procedures and should be followed through the LFU visit for Safety assessments, regardless of the reason for early treatment discontinuation (refer to Figure 1).

The end of study is defined as the last patient study visit.

Figure 1: Study Design Flow Chart



[a] The first dose of the study treatment may occur on the same calendar day as the Screening visit.
[b] The EOT visit occurs on the day or the calendar day following (+1 day) of the last dose of study treatment.
EOT, End-of-Treatment; h, hour; IV, intravenously; PO, orally; q6h, every 6 hours; TOC, Test-of-Cure.

4.2. Rationale for Study Design

The overall study design and key study-specific elements included in this protocol are in general alignment with recommendations outlined for registrational cUTI/AP trials in current regulatory guidance (FDA 2018b), Sponsor agreements with the Food and Drug Administration (FDA) throughout the TBP-PI-HBr development program and/or applicable clinical practice guidelines.

4.3. Rationale for TBP-PI-HBr Dose

The TBP-PI-HBr dosing regimen in this study (i.e., 600 mg PO q6h) is supported by pharmacodynamic (PD) modeling across both in vivo and in vitro infection models, a population PK model developed from data from both healthy adult subjects and patients with cUTI, and clinical PK/PD modeling demonstrating high predicted target attainment across the MIC90 for relevant Enterobacterales uropathogens. In addition, the dosage regimen of 600 mg q6h matches both the plasma free drug (*f*) predicted PK/PD target attainment for Enterobacterales and the urine concentration-time profile of the comparator, imipenem-cilastatin. As further described in the IB, PK/PD analyses of data from nonclinical in vitro and in vivo studies conducted by Spero Therapeutics, Inc. indicate that the PK/PD driver predictive of TBP efficacy is best described as the ratio of *f* area under the plasma drug concentration-time curve (AUC) to the minimum inhibitory concentration (MIC) adjusted for the dosing interval (*f* AUC:MIC • 1/τ).

As for other β-lactam agents, TBP is predominantly renally cleared. TBP-PI-HBr dose adjustment is required for in patients with CrCl <50 mL/min as outlined in Section 6.2.

A steady-state arithmetic mean C_{max} of 7.99 ug/mL and steady-state arithmetic mean AUC_{0-24} of 84.7 µg.h/mL for TBP from a TBP-PI-HBr dosage regimen of 600 mg PO q6h have been calculated by simulation of the patient exposure data from SPR994-301 using PK modeling. The steady-state exposure toxicology safety margins for the TBP-PI-HBr dosage regimen of 600 mg PO q6h for human compared to the no observed adverse effect level (NOAEL) dose in rat and monkey, respectively, are 9.11 and 2.75 for C_{max} and 4.48 and 1.14 for AUC.

In both species the GI effects defined the NOAEL, and the small safety margin changes from a dosage regimen of 600 mg PO q8h for human compared to the NOAEL dose in rat and monkey (8.6 and 2.6 for C_{max} and 5.1 and 1.3 for AUC, respectively) are not considered to alter the assessment of non-clinical safety particularly as these findings are reversible and monitorable, and well characterized by marketed carbapenems. Across the clinical development program, the safety profile of a 600 mg PO q8h dosing regimen of TBP-PI-HBr was consistent with that for carbapenem and the β-lactam class. The reversibility of adverse GI effects that defined the NOAEL, as well as the absence of the drug accumulation due to the short one-hour half-life, provide further reassurance that the safety profile of the 600 mg q6h PO dose regimen should be largely similar with what was previously seen in 600 mg q8h PO dose regimen.

4.4. Rationale for Comparator

Imipenem-cilastatin is a parenteral carbapenem antimicrobial approved for the treatment of cUTI/AP in many countries and is considered an empiric SOC treatment option for patients with serious bacterial infections, including cUTI/AP. Imipenem has a similar spectrum of in vitro and

in vivo antimicrobial activity to TBP-PI-HBr against common pathogens that cause cUTI/AP, including ESBL-producing Enterobacterales and certain Gram-positive uropathogens (e.g., *Enterococcus faecalis*).

Likewise, imipenem-cilastatin (500 mg IV q6h) is selected as the active comparator to TBP-PI (600 mg PO q6h) by nature of its comparable plasma, tissue, and urine PK and similar dosing frequency.

4.5. Measures to Minimize Bias: Randomization and Blinding

4.5.1. Allocation of Patients to Treatment

Once informed consent has been obtained and eligibility has been determined, site personnel will obtain a patient number from a computer-generated randomization scheme using the Interactive Response Technology (IRT). An IRT is used for study treatment management tasks. This may include, for example, randomization, study treatment supply management, inventory management and supply ordering, study treatment expiration tracking, and emergency unblinding. Patients will be identified by a unique ten-digit patient identifier (e.g., 305-XXX-ZZZZ) in which the first three digits indicate the study identifier (e.g., 305), the second three digits indicate the site number, and the final four digits indicate the number assigned at randomization by IRT. For example, the first patient randomized at site 001 will be identified by the number 305-001-0001. The Sponsor will assign site numbers.

Randomization to treatment groups will occur in a 1:1 ratio. For this study, randomization is considered to occur at the time the patient's study entry criteria is confirmed. Once a randomization number has been assigned, that number must not be used again if, for example, a patient is withdrawn from the study. If a randomization number is allocated incorrectly, the Study Monitor must be notified as soon as the error is discovered.

To ensure balance among treatment groups, the randomization will be stratified by age at informed consent (≥18 to <65 years vs. ≥65 years), baseline diagnosis (AP vs. cUTI), and presence or absence of urinary tract instrumentation at Baseline. For the purposes of stratification, Baseline Instrumentation should be considered present if the patient has a urinary tract instrument anytime from the beginning of Screening until Randomization.

4.5.2. Blinding the Treatment Assignment

This is a randomized, double-blind, double-dummy study. Access to treatment allocation will be limited to unblinded members of the study team only, such as unblinded pharmacists and/or unblinded delegates and unblinded study monitors. Identification of study team member roles and their blinding status will be detailed in the study Blinding Plan. Investigators and patients will remain blinded to each patient's assigned treatment group through the course of the study with the exception of a few select independent PK analysts to support PK model development and refinement. All study assessments will be performed by blinded study staff. In order to maintain study treatment blinding, patients will receive, in addition to their randomized active treatment (TBP-PI-HBr or imipenem-cilastatin), a matching placebo form of the active treatment to which they were not assigned. The matching placebos will look identical to the active form.

Individual participant-level, de-identified, unblinded, and scrambled (i.e., random reassignment of participant identification numbers) drug concentration information will be analyzed prior to unblinding the study. In that case, independent clinical PK analysts (who are not involved in study conduct) will have access to an unblinded scrambled population PK-specific dataset (e.g., drug concentrations, actual dosing information, demographics, and laboratory details, but no AE or efficacy data) at 1 or more time points (e.g., prior to the interim or primary analysis) throughout the study for population PK model development and refinement.

The Sponsor and its designees (CRO/vendors) responsible for monitoring safety and microbiological (i.e., pathogen identification, susceptibility data, and the number par participants eligible for the micro-ITT population) data instream will remain blinded to patient treatment assignments throughout the study. Blinded monitoring of pathogens will be conducted, to determine whether end-of-study targets are likely to be achieved. Procedures will be described in a separate evaluability review plan, and no impact on trial integrity is expected.

4.5.3. Unblinding the Treatment Assignment

The IRT will be programmed with blind-breaking instructions. Backup Code-break information is held by the unblinded pharmacist or designated unblinded person at the site and by the Contract Research Organization (CRO) Unblinded Medical Monitor for the study or unblinded designee.

Treatment assignment must not be broken during the study except in emergencies where the identification of the IP/comparator is required for further treatment of the patient. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded in the IRT and the source documents. After breaking the blind and the patient is withdrawn from study treatment, he or she should receive follow-up for safety purposes. Any code-breaks that occur must be reported to the Sponsor or its designee within 24 h.

Unblinding measures for safety will be detailed in the Medical Monitoring Plan; blinding/unblinding details of data will be detailed in the Data Management Plan; and details regarding monitoring of unblinding source documents and data will be captured in the Clinical Monitoring Plan.

Data that may potentially unblind the treatment assignment (e.g., IP/comparator concentrations, treatment allocation, and IP/comparator preparation/accountability data) will be handled with special care during the data cleaning and review process. These data points will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to unblinded quality assurance representatives or unblinded monitors for the purposes of conducting independent drug audits.

The Independent Data Monitoring Committee (IDMC) and CRO/vendors performing statistical analyses will be unblinded for the IA (refer to Section 10.1). The IDMC details will be described

in a separate charter and analysis plan. Study team members from the Sponsor and CRO who are operating the study and conducting the final analysis will remain blinded.

The Pharmacovigilance CRO may unblind the treatment assignment for any patient with a related serious adverse event (SAE). If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's treatment assignment, may be sent to investigators in accordance with local regulation and/or Sponsor policy.

5. STUDY POPULATION

5.1. Inclusion Criteria

Patients meeting all the following inclusion criteria should be considered for randomization in the study:

1. male and female patients at least 18 years of age; patients enrolled in India must be ≤90 years of age
2. able to provide informed consent (for further details regarding patient consenting, refer to Section 11.3.1)
3. able to ingest oral tablets for the anticipated treatment duration. If present at Baseline, nausea and/or vomiting should be mild or well controlled with antiemetic therapy.
4. have a diagnosis of cUTI or AP as defined below:
   a. **cUTI definition**:
      at least TWO of the following signs and symptoms:
      i. chills, rigors, or fever (oral, tympanic, rectal or core temperature >38.0°C [>100.4°F]); fever must be observed and documented by a health care provider
      ii. dysuria, urgency to void, or increased urinary frequency
      iii. nausea or vomiting, as reported by the patient
      iv. lower abdominal pain, suprapubic pain, pelvic pain, or flank pain/costovertebral angle tenderness.

      AND at least **ONE** of the following risk factors for cUTI:
      i. implanted urinary tract instrumentation (e.g., nephrostomy tube, ureteric stents, or other urinary tract prosthetic material), ongoing intermittent bladder catheterization, or presence of an indwelling bladder catheter (Note: bladder catheters that have been in place for >24 h prior to Screening must be removed or replaced prior to collection of the Screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated)
      ii. current known functional or anatomical abnormality of the urogenital tract, including anatomic abnormalities of the urinary tract, neurogenic bladder, or post-void residual urine volume of ≥100 milliliters (mL) within the past 6 months
      iii. complete or partial obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis, urethral stricture) that is expected to be medically or surgically treated during study drug therapy (prior to EOT visit)
      iv. known intrinsic renal disease with blood urea nitrogen (BUN) >20 mg/deciliter (dL), or blood urea >42.8 mg/dL, or serum creatinine (Cr) >1.4 mg/dL
      v. urinary retention, including urinary retention in men due to previously diagnosed benign prostatic hyperplasia (BPH)

b. **AP definition**:

acute flank pain (onset within 7 days prior to randomization) or costovertebral angle tenderness on physical examination **AND** at least **ONE** of the following signs and symptoms:

i. chills, rigors, or fever (oral, tympanic, rectal or core temperature >38.0°C [>100.4°F]); fever must be observed and documented by a health care provider
ii. peripheral white blood cell count (WBC) >10,000/cubic millimeter (mm^3) or bandemia (>15% immature polymorphonuclear neutrophils [PMNs], regardless of WBC count)
iii. nausea or vomiting, as reported by the patient
iv. dysuria, urgency to void, or increased urinary frequency.

Note: Patients who meet the definition for cUTI (refer to Inclusion Criterion 4.a) and have flank pain or costovertebral tenderness should be randomized as cUTI rather than AP.

5. have an adequate urine specimen for evaluation of culture obtained within 24 h prior to randomization with evidence of pyuria that includes at least one of the following:
   a. at least 10 WBCs per high power field (HPF) in urine sediment
   b. at least 10 WBCs per mm^3 in unspun urine
   c. positive leukocyte esterase (LE) on urinalysis

   Note: Patients may be randomized and administered study drug prior to knowledge of urine culture results, but pyuria must be documented.
6. expectation, in the judgment of the Investigator, that the patient will survive with effective antimicrobial therapy and appropriate supportive care for the anticipated duration of the study
7. willing to comply with all the study activities and procedures throughout the duration of the study
8. willing to agree to use a highly effective method of birth control; male patients must agree to not engage in sexual activity with a female partner that could lead to pregnancy (i.e., heterosexual vaginal intercourse) or must agree to use an effective barrier method of contraception from Screening through the LFU visit and for 90 days following the last dose; females of childbearing potential (FOCP) must have a negative pregnancy test at Screening and agree to abstain from sexual activity that could lead to pregnancy (i.e., heterosexual vaginal intercourse or in vitro fertilization) from the time of Screening through the EOT visit, or agree to use a highly effective method of contraception from the time of Screening throughout the study (through the LFU visit). Highly effective methods of birth control include one or more of the following:
   a. an approved hormonal contraceptive associated with inhibition of ovulation including oral, implantable, transdermal, injectable, or intravaginal contraceptive used consistently for at least 1 month prior to study drug dosing
   b. an intrauterine device or intrauterine hormone-releasing system

c. male sexual partner who has been vasectomized for at least 3 months prior to Screening and who has obtained a follow-up negative sperm count.

9. female of nonchildbearing potential based on at least 1 of the following criteria:
   a. post-menopausal status defined as amenorrhea for at least 12 months prior to randomization
   b. Follicle Stimulating Hormone (FSH) levels in the laboratory defined post-menopausal range; in the absence of amenorrhea for at least 12 months prior to randomization, at least two FSH measurements demonstrating levels in the post-menopausal range are required
   c. patient report of surgical sterilization (i.e., bilateral tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy) at least 6 weeks prior to randomization.

5.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be enrolled in the study:

1. presence of any known or suspected disease or condition that may confound the assessment of efficacy, including but not limited to the following:
   a. perinephric or renal corticomedullary abscess
   b. uncomplicated urinary tract infection (uUTI [acute cystitis that does not meet the cUTI disease definition; refer to Inclusion Criterion 4.a])
   c. polycystic kidney disease
   d. recent history of trauma to the pelvis or urinary tract
   e. confirmed or suspected acute or chronic bacterial prostatitis, orchitis, or epididymitis
   f. chronic vesicoureteral reflux
   g. previous or planned renal transplantation
   h. previous or planned cystectomy or ileal loop surgery
   i. known or suspected non-renal source of infection (e.g., infective endocarditis, osteomyelitis, meningitis, pneumonia)
   j. confirmed or suspected infection that is caused by a pathogen that is resistant to either study drug (e.g., carbapenem-resistant pathogen), including infection caused by fungi (e.g., candiduria) or mycobacteria (e.g., urogenital tuberculosis) or an intrinsically-resistant bacterial species not expected to respond to oral IP or comparator IV (e.g., *Pseudomonas* species)
2. gross hematuria requiring intervention other than administration of study drug or removal/placement of urinary tract instrumentation
3. urine Gram stain (if performed by site) fails to demonstrate a Gram-negative bacillus (*i.e., negative Gram stain or Gram stain demonstrating only a Gram-positive organism*)

   Note: Urine Gram stain should be performed, if possible, to inform eligibility but is not mandatory for Screening.
4. urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required for relieving an obstruction or placing urinary tract instrumentation)

5. creatinine clearance (CrCl) of ≤30 mL/minute (min), as estimated by the Cockcroft-Gault formula:

$$eC_{Cr}[mL/min] = \frac{(140 - \text{Age [yrs]}) \times \text{Body Weight [kg]} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine [mg/dL]}}$$

6. anticipated concomitant use of non-study antimicrobial drug therapy between randomization and the LFU visit that would potentially effect outcome evaluations of cUTI/AP, including but not limited to antimicrobials with potential activity against Gram-negative pathogens, antimicrobial drug prophylaxis, and antimicrobial bladder irrigation
7. receipt of a potentially effective antimicrobial within 72 h prior to study randomization
8. severe hepatic impairment at Screening, as evidenced by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5×upper limit of normal (ULN) or total bilirubin>3×ULN, or clinical signs of cirrhosis or end-stage hepatic disease (e.g., ascites, hepatic encephalopathy)
9. pregnant or lactating women
10. history of epilepsy or known seizure disorder (excluding a history of childhood febrile seizures)
11. history of proven or suspected *Clostridioides difficile* associated diarrhea
12. receipt of any investigational device or investigational medication during the last 30 days or 5 half-lives, whichever is longer, prior to randomization
13. known history of human immunodeficiency virus (HIV) infection with known CD4 count <200/mm^3 or acquired immunodeficiency syndrome (AIDS)-defining illness within the past year
14. presence of immunodeficiency or an immunocompromised condition including neutropenia (<1,000 neutrophils/mm^3 obtained from the local laboratory at Screening), hematologic malignancy, bone marrow transplant, or receiving immunosuppressive therapy such as cancer chemotherapy, medications for the rejection of transplantation, and long-term use of systemic corticosteroids (e.g., ≥20 mg/day of prednisone or systemic equivalent for at least 2 weeks)
15. QT interval corrected using Fridericia's formula (QTcF) >480 msec based on Screening electrocardiogram (ECG)
16. history of significant hypersensitivity or allergic reaction to β-lactam antimicrobials (e.g., cephalosporins, penicillins, carbapenems), product excipients (mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, colloidal silicon dioxide, and Opadry®) or any contraindication to the use of imipenem-cilastatin
17. history of known genetic metabolism anomaly associated with carnitine deficiency (e.g., carnitine transporter defect, methylmalonic aciduria, propionic acidemia)

18. requirement for concomitant use of valproic acid, divalproex sodium, or probenecid between randomization and EOT
19. unable or unwilling to comply with the protocol
20. an employee of the Investigator or study center with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as a family member of the employee or the Investigator.

6. STUDY TREATMENTS

6.1. Identity of Investigational Products

TBP-PI-HBr is the hydrobromide salt of TBP-PI, a pivoxil prodrug which rapidly converts to TBP, the active moiety, in vivo. The pivoxil prodrug formulation enables oral absorption and improved bioavailability of TBP (Kato 2010) while the hydrobromide salt formulation improves the drug substance and drug product properties, including stability. Additional details are provided in Section 2.2 and the current TBP-PI-HBr IB.

TBP-PI-HBr tablets will be administered PO as one or two 300 mg film-coated immediate-release tablets (depending on renal function). TBP-PI-HBr tablets will be supplied by a Sponsor-qualified Contract Manufacturing Company.

The comparator, imipenem-cilastatin, is a commercially available parenteral carbapenem (β-lactam antibacterial) with a similar spectrum of microbiologic activity to that described for TBP-PI-HBr. It is the combination of imipenem, the carbapenem antibacterial, and cilastatin, a renal dehydropeptidase inhibitor. Imipenem-cilastatin will be provided as a sterile, lyophilized powder for reconstitution in vials. Commercially available imipenem-cilastatin will be procured from a qualified manufacturer/vendor supplied by the Sponsor. Please refer to the SmPC (PRIMAXIN® I.V. SmPC)/ Product Package Insert (PRIMAXIN® I.V. USPI) for detailed information regarding imipenem-cilastatin.

A matching dummy/placebo infusion of normal saline solution (0.9%) and matching dummy TBP-PI-HBr tablets will be used to maintain the blind. Normal saline and matching dummy TBP-PI-HBr tablets will be supplied by the Sponsor. Standard operating procedures will be followed for the receipt, handling, and accountability of the study formulations.

A summary of the IP (TBP-PI-HBr or imipenem-cilastatin) dosage form and strength are provided in Table 2. Dosage regimens are outlined in Section 6.2.

Table 2: Summary of Investigational and Comparator Products Dosage Form and Strength

Study Treatment	Dosage Form and Strength
TBP-PI-HBr (oral IP)	300 mg green, round, biconvex, film-coated immediate-release tablets debossed with “TBP” on one side and “300” on the other side Each TBP-PI-HBr tablet contains 348.8 mg TBP PI HBr, which is equivalent to a 300 mg dose of TBP-PI containing 231 mg of TBP Clinically labeled per health authority regulations
Matching dummy TBP-PI-HBr tablets	Green, round, biconvex, film-coated tablets pressed from a blend consisting of similar inactive ingredients as active TBP-PI-HBr and uses mannitol, which replaces the active pharmaceutical ingredient (TBP)
Imipenem-cilastatin (IV comparator)	Sterile powder for reconstitution in single-dose vials containing 500 mg imipenem (anhydrous equivalent) and 500 mg cilastatin (free acid equivalent) Clinically labeled per health authority regulations
Sodium chloride injection	0.9% sodium chloride injection, 100 mL

IP, investigational product; IV, intravenous; TBP, tebipenem; TBP-PI-HBr, tebipenem pivoxil hydrobromide.

6.2. Dosing and Treatment Regimens

Eligible patients with a clinical diagnosis of cUTI/AP of sufficient severity to start empiric IV antimicrobials, and who can tolerate oral medication, will be randomized in a 1:1 ratio to receive either:

- TBP-PI-HBr 600 mg (2×300 mg film-coated tablets), administered PO q6h (±1 h) plus dummy infusion (0.9% sodium chloride) administered IV over 30 min q6h (±1 h)
- Imipenem-cilastatin, 500 mg administered IV over 30 min q6h (±1 h) plus matched dummy tablets administered PO q6h (±1 h)

The total duration of study treatment will be 7-10 days. All patients will be treated for a minimum of 7 days (i.e., will be considered to have completed therapy after the last scheduled dose on study Day 7); however, treatment may continue for up to 10 days at the discretion of the Investigator.

Each patient will receive oral dosing with TBP-PI-HBr or matched dummy/placebo tablets q6h (depending on renal function) followed by a 30-minute infusion of imipenem-cilastatin or matched dummy infusion every 6h as outlined below.

Both TBP-PI-HBr and imipenem-cilastatin require dosage adjustment in the setting of renal insufficiency as outlined in Section 6.2.1 and Section 6.2.2, respectively. Additional details regarding post-Baseline monitoring of CrCl and dosage adjustment are provided in Section 6.3.1.

Note: Dosage adjustments by CrCl category are different for the oral IP and IV comparator.

Renal function as estimated by CrCl will be assessed using the Cockcroft-Gault formula (Cockcroft 1976) as outlined below using serum Cr levels obtained at the local laboratory at Screening (Baseline) and throughout the study:

Cockroft-Gault Formula:

$$\mathrm{eC_{Cr}[mL/min]} = \frac{(140 - \text{Age [yrs]}) \times \text{Body Weight [kg]} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine [mg/dL]}}$$

Actual weight in kilograms (not ideal weight) is required for the CrCl calculation. If available, the weight obtained on the day of the serum Cr measurement should be used for calculating CrCl; however, the Baseline weight may be used throughout the study for CrCl estimations if repeated weights cannot be obtained. The weight used to calculate CrCl will be recorded in the electronic case report form (eCRF).

Dosing of oral IP tablets may be administered irrespective to the timing of meals.

6.2.1. TBP-PI-HBr Dosing in Patients with CrCl >50 mL/min

Patients randomized to receive TBP-PI-HBr with estimated Baseline CrCl >50 mL/min will receive TBP-PI-HBr 600 mg (two 300 mg tablets) PO q6h (±1 h) plus dummy (0.9% normal saline) IV infusion administered in a total volume of 100 mL over 30 min q6h (±1 h).

Dose adjustment is required for patients with estimated Baseline CrCl ≤50 mL/min as outlined in Section 6.2.1.1. However, for patients who have a Screening/Baseline CrCl near the 50 mL/min

threshold (i.e., 45-50 mL/min) in whom the CrCl is expected to increase to >50 mL/min over the first day of therapy (e.g., after IV fluid hydration in patients who are volume depleted in setting of acute infection), the Investigator may choose to administer TBP-PI-HBr 600 mg while reassessing the need for a dosage adjustment based on a subsequent CrCl assessment (refer to Section 6.2.1.1 for details).

6.2.1.1. TBP-PI-HBr Dose Adjustments in Patients with Impaired Renal Function (CrCl ≤50 mL/min)

TBP-PI-HBr dosage adjustment is required for patients with CrCl ≤50 mL/min as outlined in Table 3. Data supporting the dosage adjustments in patients with impaired renal function are provided in the IB.

Table 3 TBP-PI-HBr Dosage Regimen by Estimated Creatinine Clearance Category

CrCl (mL/min)[a]	TBP-PI-HBr Dosage	TBP-PI-HBr (300 mg) Dummy/Placebo
>50	600 mg PO q6h	two tablets PO q6h (±1 h)
>30 to ≤50	300 mg PO q6h	one tablet PO q6h (±1 h)

Note: For patients with moderate/severe renal insufficiency who have a Screening/Baseline CrCl near the threshold of mild renal insufficiency (i.e., 45-50 mL/min for moderate renal insufficiency) in whom the CrCl is expected to increase above the threshold (e.g., >50 mL)/min over the first day of therapy (e.g., after IV fluid hydration), the Investigator may choose to administer TBP-PI-HBr dosage of 600 mg while reassessing the need for a dosage adjustment based on a subsequent CrCl assessment.

[a] As estimated by Cockroft-Gault Formula.

CrCl, creatinine clearance; h, hour; mL, milliliter; min, minute; PO, orally; TBP-PM-HBr, tebipenem pivoxil hydrobromide; q6h, every 6 hours.

6.2.2. Imipenem-cilastatin Dosing in Patients with CrCl ≥90 mL/min

Patients randomized to receive imipenem-cilastatin with estimated Baseline CrCl ≥90 mL/min will receive 500 mg IV over 30 min q6h (±1 h) plus matched dummy TBP-PI-HBr tablets administered PO q6h (±1 h).

Dose adjustment is required for patients with estimated Baseline CrCl <90 mL/min as outlined in Section 6.2.2.1. However, for patients who have a Screening/Baseline CrCl near the 90 mL/min threshold (i.e., 85-90 mL/min) in whom the CrCl is expected to increase to >90 mL/min over the first day of therapy (e.g., after IV fluid hydration), the Investigator may choose to administer imipenem-cilastatin 500 mg while reassessing the need for a dosage adjustment based on a subsequent CrCl assessment (refer to Section 6.2.1.1 for details).

6.2.2.1. Imipenem-cilastatin Dose Adjustments in Patients with Impaired Renal Function (CrCl <90 mL/min)

Imipenem-cilastatin dosage adjustment is required for patients with CrCl <90 mL/min as outlined in Table 4, consistent with the product labeling (Primaxin I.V. USPI, Primaxin I.V. SmPC).

Table 4: Imipenem-cilastatin Dosage Regimen by Estimated Creatinine Clearance Category

CrCl (mL/min)[a]	Imipenem-cilastatin dosage
≥90	500 mg IV q6h
≥60 to <90	400 mg IV q6h
>30 to <60	300 mg IV q6h

Source: Primaxin I.V USPI.
CrCl, creatinine clearance; h, hour(s); IV, intravenous; min, minute; q6h, every 6 hours.

6.3. Timing of Dose Administration

Early delivery of antimicrobial therapy is critical to efficacy outcomes, thus the first dose of oral and IV study therapy should be administered as soon as possible following randomization on Day 1. The oral and IV doses may be administered simultaneously or if consecutive, the oral IP should directly precede dosing of IV comparator administration.

Following the first dose of either IP or comparator, a one-time dose adjustment (of the second dose only) is allowed, to align with site-specific medication dosing schedules. Exceptions are made in the case of a post-Baseline adjustment in dosing due to change in CrCl (refer to Section 6.3.1). The dosing interval adjustment must be such that the next dose of oral IP is administered a minimum of 4 h after the preceding dose and a maximum of 8 h (±1 h) after the preceding dose, and the next dose of IV comparator (if adjusted) must be administered within 4 h of its planned dosing schedule. Additional doses may be adjusted within the protocol-defined window of ±1 h per dose.

As study days are defined as calendar days, every effort should be made to complete administration of both IP or comparator doses within the same calendar day (e.g., avoid starting a dose of IP/comparator before midnight [00:00] and stopping the dose after midnight).

6.3.1. Monitoring of CrCl during Investigational Product Therapy

Patients with cUTI/AP are at risk for volume depletion, fluctuating renal function, renal insufficiency and/or acute kidney injury; therefore, study patients require frequent monitoring of their renal function while on antimicrobial therapy to determine the need for IP/comparator dosage adjustment based on a change in renal function category at any time during the treatment period from Baseline to last dose of IP/comparator.

Estimated CrCl should be calculated based on local laboratory assessment of serum creatinine according to the frequency outlined below:

- **For patients with Baseline CrCl ≥90 mL/min and presumed stable renal function**, serum Cr and estimated CrCl should be assessed at least every 3 days and the necessary dosage adjustments made as outlined in Table 3 or Table 4 for any decrease in CrCl <90 mL/min.

- **For patients with CrCl <90 mL/min or patients suspected to have fluctuating renal function**, serum Cr and estimated CrCl should be assessed *at least once daily* (QD) from the time of first dose until the CrCl stabilizes (i.e., no change CrCl category) over 3 consecutive daily measurements in order to determine whether a dosage adjustment as outlined in Table 3 or Table 4 is necessary.
- **For all patients:** If the CrCl changes to a value that falls within 5 mL/min of the threshold requiring a change in IP/comparator dosing, the Investigator may choose to implement the dosage adjustment or continue to monitor the patient and reassess the need for a dosage adjustment based on a subsequent CrCl assessment.

If a post-Baseline dosage adjustment is determined necessary, the Investigator should inform the pharmacist immediately so that the appropriate changes to IP/comparator may be implemented within approximately 24 hours when the next doses of IP/comparator are prepared.

Note: Patients with Baseline CrCl ≤30 mL/min are excluded from the study (refer to Exclusion Criterion 5). After randomization, if the estimated CrCl decreases to ≤30 mL/min during the treatment period, further dosing of IP/comparator should be suspended and a repeat serum Cr measurement and recalculated CrCl performed to verify the need for IP/comparator discontinuation. If the repeated CrCl is ≤30 mL/min, IP/comparator should be discontinued.

6.4. Treatment Compliance

6.4.1. Dosing Interruptions, Incomplete Doses, and Missed Doses

All instances of noncompliance with the pre-specified dosage regimens (refer to Section 6.2.1 [for TBP-PI-HBr] and Section 6.2.2 [for imipenem]) will be documented as protocol deviations, including dosing interruptions (dosing paused or temporarily suspended for any reason), incomplete doses, missed doses, or doses administered out of window.

If planned dosing of oral IP or IV comparator is missed for any reason, the planned dose should be administered as quickly as possible at the time of discovery if clinically feasible based on the patient's continued ability to tolerate oral IP and/or IV comparator dosing, with the following adjustment to the dosing schedule.

For missed or delayed oral IP doses:

- If the dose is administered *within* 4 h of its intended dosing time, the subsequent doses should be administered at the pre-planned q6h intervals as originally scheduled.
- If the dose is administered *after* 4 h of its intended dosing time, the remaining doses should be administered according to a new q6h regimen starting with the timing of the restarted oral IP administration.

If a patient vomits within 30 min of oral IP dose administration, the oral IP dose should be re-administered as soon as possible following resolution of nausea and/or administration of antiemetics and the subsequent dosing schedule adjusted as noted above. If the patient vomits after 30 min of oral IP dose administration, subsequent dose administration should proceed according to the original dosing schedule.

For missed or delayed IV comparator doses:

1. If the dose is administered *within* 4 h of its intended dosing time, the remainder of the doses should be administered at the pre-planned q6h intervals (i.e., the previous q6h dosage interval should remain as scheduled).
2. If the dose is administered *after* 4 h of its intended dosing time, the remainder of the doses should be administered in a new q6h regimen starting with the timing of the restarted IV comparator administration.

If dosing of IV comparator is interrupted or incomplete, no adjustment to the dosing schedule is required.

Investigators are encouraged to discuss continued comparator administration options after interrupted dosing, incomplete, or missed doses with the Medical Monitor on a case-by-case basis.

6.4.2. Treatment Administration

Oral IP and IV comparator will be administered by qualified facility personnel at the site. The date and time of administration of oral IP or IV comparator will be recorded in the CRF along with the start and stop time of IV comparator.

The Investigator or his/her designee (as documented by the Investigator in the applicable study delegation of authority form) will administer the IP/comparator only to patients included in this study following the procedures set out in the study protocol. Each patient will be given only the treatment-assignment IP or comparator. All IP/comparator administrations will be documented on the CRFs and/or other IP/comparator record.

6.4.3. Drug Accountability

Investigators will be provided with sufficient amounts of the IP/comparator to carry out this protocol for the agreed number of patients. The Investigator or designee will acknowledge receipt of the IP/comparator documenting shipment content and condition. Accurate records of all IP/comparator dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

Drug accountability must be assessed at the container/packaging level for unused IP/comparator that is contained within the original tamper-evident sealed container or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

No IP/comparator stock or returned inventory from a Spero Therapeutics Inc., sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor. The Sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records if the blind of the study is not compromised.

At the end of the study, or as instructed by the Sponsor, all unused stock and empty/used IP/comparator packaging are to be sent to a nominated contractor on behalf of the Sponsor. Any unused IP/comparator stock being returned to the Sponsor’s designated contractors must be counted and verified by clinical site personnel and the Sponsor or designee. For unused supplies

where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. All certificates of delivery/drug receipts should be signed by the site representative to confirm contents of shipment. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems do not require a shipment form. Returned IP/comparator stock must be packed in a tamper-evident manner to ensure product integrity. Contact the Sponsor for authorization to return any IP/comparator stock prior to shipment. Shipment of all returned IP/comparator stock must comply with local, state, and national laws.

With the written agreement of the Sponsor, at the end of the study all unused stock and empty/used IP/comparator packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how must be obtained with copies provided to the Sponsor. Destruction of IP/comparators stock must be in accordance with local, state, and national laws.

Based on entries in the site-drug accountability forms, it must be possible to reconcile IP/comparator stock delivered with those used and returned. All IP/comparator must be accounted for and all discrepancies investigated and documented to the Sponsor's satisfaction. Procedures for return or destruction of both the used and unused IP/comparator stock will be described in the drug distribution plan.

6.5. Storage

TBP-PI-HBr 300 mg film-coated tablets are dispensed in a sealed, light-resistant container. Both IP and comparator supplies must be stored as labeled in a secure area with access limited to the Investigator and authorized staff. IP and comparator supplies will be stored securely under the appropriate conditions detailed in the pharmacy manual and according to local standard operating procedures. The Investigator has overall responsibility for ensuring that IP/comparator supplies are stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or members of the study team, but this delegation must be documented.

Temperature monitoring is required at the storage location to ensure that the IP/comparator supplies are maintained within an established temperature range (refer to the Pharmacy Manual). The Investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained.

The temperature should be either monitored continuously by using an in-house system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific period can be recorded and retrieved as required. Such a device (e.g., certified min/max thermometer) would require manual resetting upon each recording.

The Sponsor must be notified upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The Sponsor will determine the ultimate impact of any product temperature excursions and will provide supportive documentation as necessary. Under no circumstances should any product be dispensed to patients until the impact is determined and deemed appropriate for use by the Sponsor.

6.6. Prior and Concomitant Therapy

Review of medical history during screening or while on study will capture prior and/or concomitant receipt of any pharmacologic and/or non-pharmacologic treatments (including over-the-counter [OTC] treatments such as herbal treatments, vitamins, diet aids, and hormone supplements) in addition to medications received within 30 days prior to the data of first dose of IP or comparator.

6.6.1. Prohibited Concomitant Medications

Concomitant administration of non-study, potentially effective, systemic antimicrobial therapy that would potentially confound the assessment of treatment outcomes is not allowed (between randomization and LFU), except in cases of cUTI/AP study treatment clinical failure.

Topical antimicrobials and antimicrobials for the treatment of *Clostridioides difficile* infection are permitted. For treatment of new and unexpected infections other than cUTI/AP (i.e., adverse events [AEs]), narrow spectrum antimicrobials which are not expected to have potential to treat the causative pathogen(s) for cUTI/AP should be selected whenever possible.

Questions regarding the use of concomitant non-study-specific systemic antimicrobial therapy should be directed to the Medical Monitor prior to administration.

Treatment with any of the following concomitant medications is prohibited between randomization and the end of therapy due to potential drug-drug interactions with either IP or comparator agent:

- Valproic acid or divalproex sodium
- Probenecid
- Ganciclovir or valganciclovir

As noted in Section 2.2.3, the potential for drug-drug interactions with TBP-PI-HBr is otherwise low. As noted in Inclusion Criterion 3, TBP-PI-HBr may be co-administered with antiemetic therapy in order to control nausea and/or vomiting if present at Baseline.

All instances of noncompliance with prohibited concomitant therapies will be documented as protocol deviations.

6.7. Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal

6.7.1. Withdrawal from Study

Patients may withdraw from the study or be withdrawn at the request of the Investigator or Sponsor at any time. Examples of reasons for study withdrawal include:

- the patient withdraws consent or requests withdrawal from the study for any reason
- the patient is lost to follow-up
- the patient fails to comply with protocol requirements or study-related procedures

- the Investigator determines that it is in the best interest of the patient to withdraw from the study protocol, for reasons other than an AE
- the study is terminated or temporarily suspended by the Sponsor or a Regulatory Authority (RA) for any reason, including but not limited to IP-related or comparator-related unexpected life-threatening SAEs detected during safety monitoring (e.g., Torsade des Pointes or other ventricular arrhythmias).

Patients who wish to withdraw completely from this clinical study during the treatment period should be encouraged to undergo EOT safety and efficacy assessments at the time of withdrawal.

Patients who are withdrawn from the study will not be replaced.

6.7.2. Premature Discontinuation of Study Treatment

Premature discontinuation of study treatment by the Investigator is an important discussion, which should include the Medical Monitor, if feasible, before the IP or comparator is discontinued.

Possible reasons for premature discontinuation from IP or comparator due to safety reasons include, but are not limited to, the following: occurrence of an AE that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from study treatment administration; Hy's law criteria are met, defined by at least 3-fold elevations of ALT or AST above the ULN, elevation of serum total bilirubin to >2 times ULN without elevated serum alkaline phosphatase (ALP), and no other disease or condition can be found to explain the liver test abnormalities; or known pregnancy or breastfeeding during the study treatment administration period; decline in post-Baseline renal function such that the estimated CrCl falls to ≤30 mL/min (refer to Section 6.3.1).

Patients prematurely discontinued from IP or comparator for any reason and for whom further antimicrobial therapy is not required for treatment of the primary infection (e.g., the cUTI/AP has resolved completely or improved to the point where no further antimicrobial therapy is necessary), may be assessed as a clinical cure. Patients prematurely discontinued from study treatment who require further antimicrobial therapy for the cUTI/AP should be assessed as a clinical failure.

Possible reasons for discontinuation from study treatment due to insufficient therapeutic effect include, but are not limited to, clinical worsening or lack of clinical progress. If the Investigator deems the benefit-to-risk ratio of study treatment continuance acceptable, IP or comparator administration of at least 48 h is encouraged before discontinuation from study treatment for insufficient effect.

Refer to the EOT visit procedures (refer to Section 7.1.3) regarding the clinical assessment of patients who prematurely discontinue IP. Patients who are prematurely discontinued from IP or comparator administration for the reasons other than study consent withdrawal should remain in the study and continue to undergo study assessments at every subsequent study visit (e.g., TOC, LFU), and should *not* be withdrawn from study.

6.7.3. Patients Lost to Follow-up Prior to Last Scheduled Visit

At least 3 documented attempts must be made to contact any patient lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). One of these documented attempts must include a written communication sent to the patient's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations.

7. STUDY PROCEDURES AND OUTCOME ASSESSMENTS

7.1. Study Visits

Refer to Schedule of Assessments (SOA; Appendix 2) for details regarding the study visits and procedures.

The duration of study participation for each patient is approximately 28 days.

7.1.1. Screening Visit (Day -1 or 1)

Day -1 to 1: Screening procedures must be performed within 24 h prior to randomization on Day 1 to determine study eligibility.

Standard-of-care (SOC) assessments performed at the site within the Screening period (within 24 h of randomization) may be used to determine patient eligibility even if performed prior to signing the informed consent form (ICF). Other routine clinical assessments may be used to determine eligibility if performed prior to informed consent but within the 24-hour Screening period.

Note: bladder catheters that have been in place for >24 h prior to Screening must be removed or replaced prior to collection of the screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated

Specifically, the following assessments may be used in determining study eligibility if performed prior to signing the ICF but within the 24-hour Screening window:

- medical and surgical history (refer to SOA footnote e) including review of urinary tract instrumentation status (refer to SOA footnote q)
- prior and concomitant medications review
- complete physical exam (consist of skin, head and neck, heart, lung, abdomen (including suprapubic area), extremities, back/flank/costovertebral angle tenderness, and neuromuscular assessments)
- vital signs (including blood pressure [BP], pulse [P], respiratory rate [RR], and temperature [T]) (refer to SOA footnote g)
- cUTI/AP symptoms and signs
- local serum Cr and calculated CrCl for dose adjustments (refer to SOA footnote j)
- urine Gram stain and culture collection (Gram stain is optional, but should be done when possible, to confirm eligibility); refer to SOA footnote l
- blood culture collection: 2 sets of blood cultures (each set is 1 aerobic and 1 anaerobic (if possible) blood culture bottle) from 2 separate venipuncture sites to be collected at Screening. Blood cultures should be repeated on the day that a previous (e.g., Baseline) blood culture is determined to be positive (e.g., reveals growth of a pathogen). Blood cultures should be repeated as necessary until negative blood cultures are obtained (refer to SOA footnote m).

- Local labs for safety and pregnancy testing (refer to SOA footnote i)
- Single 12-lead ECG (refer to SOA footnote h)

Study specific Screening assessments, including blood and urine (for safety) collected for analysis by the central laboratory (refer to SOA footnote k), must be performed after signing the ICF.

7.1.2. Treatment Visits (Days 1 up to 10)

Treatment Visits, Day 1 up to Day 10: Patients receive IP (TBP-PI-HBr) or comparator (imipenem-cilastatin) and dummy infusions or matched dummy tablets during this treatment period. The first treatment with the IP or comparator may occur on the same calendar day as the Screening visit or on the next calendar day. Day 1 is the first day of study treatment administration. The duration of study treatment will be 7-10 calendar days.

If the Screening visit and Day 1 occur on the same calendar day, the physical exam, vital signs, and assessment of cUTI/AP clinical signs and symptoms do not need to be repeated twice in the same calendar day (repeated assessments within the same calendar day are optional). However, separate Screening and Day 1 ECGs must be performed per the protocol SOA, as Day 1 ECGs are timed from the first dose of study treatment (refer to SOA footnote h).

Specifically, if Screening visit and Day 1 occur on the same calendar day:

- complete physical exam at Screening is required, while Day 1 focused physical exam is optional (refer to SOA footnote a)
- vital signs at Screening are required, while repeated Day 1 vital signs are optional. If repeated vital signs are collected, record the highest daily temperature in the eCRF day (refer to SOA footnote a)
- assessment of cUTI/AP clinical signs and symptoms at Screening is required, while Day 1 assessment of clinical signs and symptoms is optional day (refer to SOA footnote a)
- *separate Screening and Day 1 ECGs must be performed.* For Screening ECGs, perform single 12-lead ECGs for assessment of eligibility. Repeat single 12-lead ECGs will be performed on Day 1 and at the EOT visit 1 h (±15 min) after oral IP dose administration and as clinically indicated (refer to SOA footnote h).

For a complete summary of treatment assessments during study Days 1-10, please see the SOA (refer to Appendix 2).

7.1.3. End-of-Treatment (EOT) Visit

The EOT visit will be completed on the last day of study treatment administration, or the following day, allowing a one-day window to complete the EOT procedures, or when a patient prematurely discontinues treatment (refer to Section 6.7). An exception is the EOT ECG which must be performed 1 h [±15 min] after the last dose. The EOT visit and procedures should be performed regardless of whether the patient completes the full course of treatment (e.g., 7-10 days) or discontinues study treatment early. Decision on treatment completion and total

treatment duration should be made by the Investigator based on his/ her clinical judgment of the clinical status of the patient (e.g., resolution or significant improvement of signs and symptoms of cUTI/AP that were present at Baseline such that no further antibacterial treatment is warranted). Patients requiring more than 10 days of treatment will be discontinued from either IP or comparator treatment. Patients receiving less than 7 days of treatment (i.e., discontinuation before the last dose on study Day 7) will be considered early withdrawal or treatment discontinuation (refer to Section 6.7.1). The patients should remain in the study for the remaining visits unless they have withdrawn consent for study participation.

7.1.4. Test-of-Cure (TOC) Visit (Day 17 ±2 Days)

The TOC Visit is Day 17 (±2 days) for all patients. A complete summary of TOC visit assessments is presented in the SOA (refer to Appendix 2).

7.1.5. Late Follow-Up (LFU) Visit (Day 28 ±2 Days)

The LFU visit is Day 28 (±2 days) for all patients. A complete summary of LFU visit assessments is presented in the SOA (refer to Appendix 2).

7.1.6. Additional Care of Patients after the Study

No after care is planned for patients in this study.

7.2. Outcome Assessments

7.2.1. Efficacy Assessment and Outcome Definitions

Efficacy will be evaluated through assessment of post-Baseline clinical outcomes (signs and symptoms of cUTI/AP), and post-Baseline microbiological outcomes (based on available urine and/or blood culture data) at each study visit (refer to SOA, Appendix 2).

Overall response (combined clinical cure plus favorable microbiological response) at TOC in the micro-ITT Population (primary endpoint); and at EOT, TOC, and LFU visits will be assessed in the micro-ITT Population and ME Populations (secondary endpoint) where:

- Clinical cure is defined as a complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antibacterial therapy is warranted, and patient is alive
- Favorable microbiological response (microbiological eradication) is defined as a reduction of Baseline uropathogens to $<10^3$ CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline and patient is alive.

Patients who require non-study antibacterial therapy for treatment of the index infection prior to assessment will be assessed as clinical failure at subsequent visits.

7.2.1.1. Investigator Assessment of Clinical Outcomes at EOT, TOC and LFU

Based on the assessment of signs and symptoms, the Investigator will choose one of the following clinical outcomes at the EOT and TOC visits:

- Clinical cure: patient is alive with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antibacterial therapy is warranted, and patient is alive
- Clinical failure: symptoms of cUTI or AP present at study entry have not completely resolved or new symptoms have developed and require the initiation of a non-study antibacterial drug therapy, or death
- Clinical indeterminate: insufficient data are available to determine if the patient is a cure or failure.

Patients deemed clinical failures at EOT, or TOC should be considered for further diagnostic workup, including urinary tract imaging (e.g., ultrasound), to assess for undiagnosed anatomical, obstructive, or neurogenic abnormalities, according to the best clinical judgment of the Investigator.

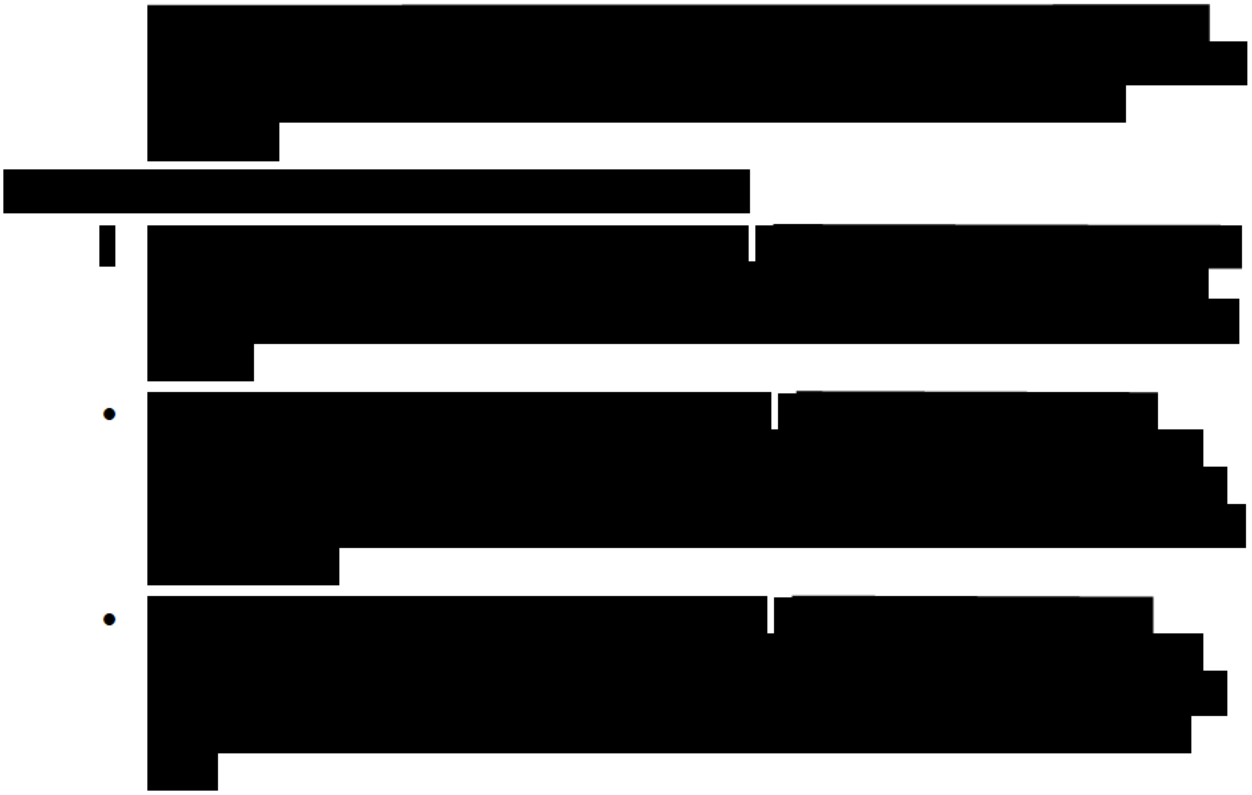
All patients will be evaluated for clinical response outcome at the LFU visit based on the assessment of signs and symptoms as:

- Cure, including sustained clinical cure: Sustained clinical cure is defined as met criteria for clinical cure at TOC, and remained free of new or recurrent signs and symptoms of cUTI or AP at LFU visit such that no further antibacterial therapy is warranted
- Failure, including clinical relapse: Clinical relapse is defined as met criteria for clinical cure at TOC, but new signs and symptoms of cUTI or AP are present at the LFU visit and the patient requires antibacterial therapy for the cUTI
- Clinical indeterminate: insufficient data are available to determine if the patient is a sustained clinical cure or clinical relapse.

Note: If a patient is assessed as a clinical failure at EOT, the patient is automatically considered a failure at the TOC and LFU visits. If a patient is assessed as a clinical failure at TOC, the patient is automatically considered a failure at the LFU visit.

[redacted]

[redacted]



7.2.2. Microbiological Assessment

Microbiological assessment will be performed with urine Gram stains and cultures, and blood cultures. All microbiological assessments will be initiated at the local or regional laboratory, including specimen collection, analysis of isolates, and shipment of isolates. Additional details with regard to handling and processing of microbiological specimens at the local or regional laboratory vs. Central Microbiology Laboratory are provided in a laboratory manual.

Urine and blood samples will be collected at the investigative site and transported to a regional or local laboratory within 24 h of collection. Upon receipt, urine samples will be processed for microbiological assessments including Gram stain (where feasible) and culture. Gram stain is performed at the site where possible to inform eligibility. The blood samples will be processed for aerobic and anaerobic (where possible) culture. Additional details regarding handling and processing of microbiological specimens at the local or regional laboratory vs. central microbiology laboratory are provided in a Laboratory Manual.

At the regional or local laboratory pathogens from urine will be quantified to determine the number of colony forming units (CFU)/milliliter (mL). Urine and blood pathogens will be identified to genus and species, and local antimicrobial susceptibility testing may be performed per local standard-of care (including carbapenem susceptibilities). All Baseline or post-Baseline urine culture isolates that grow $\geq 10^3$ CFU/mL and all blood culture isolates will be shipped to the central microbiology laboratory for identification confirmation (genus and species) and susceptibility testing for TBP, imipenem and other comparator agents and storage for possible further molecular characterization of the microorganisms.

Although local susceptibility testing is not a requirement, when local susceptibility testing indicates non-susceptibility to study treatment (e.g., intermediate susceptibility or resistance to a carbapenem antibacterial) but the patient is stable or clinically improving, the patient should remain on blinded study treatment at the Investigator's discretion. Similarly, if Baseline blood cultures become positive after randomization but the patient is stable or clinically improving, the patient should remain on blinded study treatment at the Investigator's discretion. In such cases, prior to premature discontinuation from study treatment, the Investigator should discuss the cases with the Medical Monitor. Premature discontinuation of study treatment is further discussed in Section 6.7.

[redacted]

7.2.2.2. Blood Cultures

At Screening, two sets of blood cultures (i.e., one aerobic blood culture bottle and one anaerobic (if possible) blood culture bottle from two separate venipuncture sites for a total of four bottles) must be collected.

Blood cultures should be repeated on the day that a previous (e.g., Baseline) blood culture is determined to be positive (e.g., reveals growth of a pathogen). Blood cultures should be repeated as necessary until negative blood cultures are obtained.

Culture results are to include identification of pathogens to the level of genus and species. As described in the laboratory manual, susceptibility testing for TBP will not be available to the local laboratory; TBP susceptibility will be assessed at the central laboratory. Therefore, decisions related to patient care (e.g., study treatment discontinuation) will be based on the evolution of the clinical signs and symptoms of the index cUTI or AP. All isolates cultured from blood samples (whether Screening or post-Baseline), with the exception of "contaminants" listed in Section 7.2.2.1, are to be sent to the central laboratory for identification verification and susceptibility testing. Either an automated system or a manual system can be used for blood cultures according to the preference of the local/regional microbiological laboratory performing the testing. Refer to the laboratory manual for details.

7.2.3. Safety Assessment

7.2.3.1. Medical/Surgical and Prior/Concomitant Medication History

The medical/surgical history of the patient (including urological history and any active/inactive conditions diagnosed within the previous 5 years) will be obtained at the Screening visit. Specific information will be recorded on the CRF relating to any prior or existing medical conditions/surgical procedures involving the following: infectious diseases (including viral infections, like Hepatitis and HIV), allergies, metabolic/endocrine/nutritional, hematopoietic, musculoskeletal, dermatologic, Head, Ears, Eyes, Nose, and Throat (HEENT), breasts, respiratory, cardiovascular, GI/hepatic, genitourinary/renal, neurological, urological and psychiatric/psychosocial.

Data related to the current infection under study **must not** be recorded in the medical history page of the CRF but instead in the signs and symptoms pages of the CRF.

History of prior and concomitant medications will be recorded in the CRF at the Screening visit.

7.2.3.2. Physical Examination

Abnormalities identified at the Screening visit (Day -1 or 1) will be documented in the patient's source documents and on the medical history CRF. Height and weight will be taken during the Screening physical exam. Complete physical examinations at Screening, EOT, TOC, and LFU consist of skin, head and neck, heart, lung, abdomen (including suprapubic area), extremities, back/flank/costovertebral angle tenderness, and neuromuscular assessments. Focused (limited)

physical examinations between Day 1 and EOT are symptom-based assessments. If the Screening visit and Day 1 occur on the same calendar day, the focused physical exam on Day 1 is optional. Standard-of-care (SOC) assessments performed at the site within the Screening period (within 24 h of randomization) may be used to determine patient eligibility even if performed prior to signing the ICF.

7.2.3.3. Adverse Event Collection

At each study visit, following first study treatment administration, patients will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?"). Adverse events will be collected from the time of the first dose of study treatment. Assessment and management of AEs is further discussed in Section 8.

7.2.3.4. Vital Signs

Vital sign assessments include blood pressure (BP), pulse (P), respiratory rate (RR), and temperature (T). In cases where temperature has been measured multiple times in a single day, maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be collected at Screening, daily Day 1 through EOT (prior to daily IV infusions for imipenem- cilastatin or placebo-IV treated patients), TOC, and LFU. If the Screening visit and Day 1 occur on the same calendar day, repeated vital signs on Day 1 are optional. Standard-of-care (SOC) assessments performed at the site within the Screening period (within 24 h of randomization) may be used to determine patient eligibility even if performed prior to signing the ICF. Body temperature may be taken per the site's preferred method but limited to oral, tympanic, rectal, or core measurements. The same method of measuring a patient's body temperature should be used throughout the study. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any CS deviations from Baseline vital signs, which are deemed CS in the opinion of the Investigator, will be recorded as an AE.

7.2.3.5. Clinical Laboratory Evaluations

The name and address of each clinical laboratory used in this study will be maintained in the Investigator files at each site.

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges supplied by the laboratory are used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not CS. Abnormal clinical laboratory values, that are unexpected or not explained by the patient's clinical condition may be, at the discretion of the Investigator or Sponsor, explained or resolved as soon as possible.

Laboratory Assessments for Eligibility

Local/regional laboratory results from blood and urine samples collected at Screening are used to determine eligibility (results can be from samples obtained up to 24 h prior to randomization).

The SOC assessments performed at the site within the Screening period (within 24 h of randomization) may be used to determine patient eligibility even if performed prior to signing the ICF. Assessments include serum Cr (for CrCl calculation), ALT, AST, total bilirubin, absolute neutrophil count, BUN (or blood urea), and urinalysis with microscopy.

Central Laboratory Assessments for Safety

The central safety lab will perform the following evaluations on blood and urine samples on Screening, Day1 (if the Screening central laboratory samples are collected on Day 1, the Day 1 safety laboratory samples do not need to be repeated), Day 3, Day 5, Day 7, Day 9 (if still receiving IP or comparator), EOT, TOC, and LFU:

- hematology (hemoglobin [Hb], hematocrit, red blood cell [RBC] indices)
- thrombocyte count (platelets)
- reticulocyte count
- white blood cell (WBC) count with differential (including neutrophils, eosinophils, basophils, lymphocytes and monocytes)
- coagulation (prothrombin time, international normalized ratio, activated partial thromboplastin time)
- blood chemistry:
  - electrolytes (sodium, potassium, chloride, bicarbonate)
  - non-fasting glucose
  - blood urea nitrogen (BUN)
  - creatinine (Cr) (including calculated CrCl using Cockcroft-Gault formula)
  - l-carnitine
- creatine kinase
- urate
- phosphate
- total calcium
- cholesterol
- albumin
- total protein
- total bilirubin
- conjugated bilirubin
- gamma-glutamyl transferase
- alanine aminotransferase (ALT)

- aspartate aminotransferase (AST)
- alkaline phosphatase (ALP)
- lactate dehydrogenase
- triglycerides
- complete urinalysis (pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocytes).

Note: Microscopic urinalysis will be performed, if indicated, and to include WBC, RBC, epithelial cells, and bacteria testing.

7.2.3.6. Pregnancy Testing

A urine or serum beta human chorionic gonadotropin (β-HCG) pregnancy test (according to local SOC) is performed by the local laboratory on all females of childbearing potential (FOCP) at the Screening visit and if pregnancy is suspected at any time.

In addition, a serum beta human chorionic gonadotropin (β-HCG) pregnancy test is performed by the central laboratory on all FOCP at the Screening visit and at the patient's final visit (LFU visit or time of early withdrawal from the study) (refer to SOA, Appendix 2).

7.2.3.7. Electrocardiograms

At Screening, perform a single 12-lead ECG. Repeat single 12-lead ECGs will be performed on Day 1 (after the first dose of oral dose administration) and the EOT visit (after the last dose of oral dose administration) 1 h (±15 min) after oral dose administration, and as otherwise clinically indicated after oral.

7.2.4. Pharmacokinetics Assessment

7.2.4.1. Blood Sampling for Plasma Pharmacokinetics

Blood samples will be collected for the measurement of plasma TBP.

Intensive blood sampling for plasma PK assessment will be performed in a subset of patients (at selected sites; approximately 40 patients, 20 per treatment group, 7 samples per patient). This is optional for the patient and will require a separate consent.

Blood samples for intensive PK sampling (7 samples per patient) will be collected following any oral dose on Day 2 or Day 3 (fifth, sixth, seventh, or eighth dose) at the following time intervals after oral dose administration: at 15 min (±2 min), 30 min (±5 min), 1 h (±5 min), 1.5 h (±5 min), 2 h (±10 min), 4 h (±10 min), and 6 h (±15 min but prior to the next scheduled dose).

Sparse PK sampling will be performed for all other patients. Blood samples using sparse sampling (3 samples/patient) will be collected following any oral dose on Day 2 or Day 3 (fifth, sixth, seventh, or eighth dose) at the following time intervals after oral dose administration of IP: 1 h (±15 min), 4 h (±0.5 h), and 6 h (±1 h but prior to the next scheduled dose).

The exact dose time and the exact (actual) blood sample collection time should be collected for all patients when collecting blood samples. TBP plasma concentration-time data from TBP-PI-HBr-treated patients will inform a Population PK model to be used for estimation of individual TBP PK profiles, to be separately reported. Refer to the laboratory manual for detailed instructions on sample processing, storage, and shipping.

Blood samples from TBP-PI-HBr-treated patients will be assayed by validated tandem mass spectrometry (liquid chromatography tandem mass spectrometry [LC/MS/MS]) methods for the determination of plasma TBP concentrations. Selected comparator samples may be analyzed at the request of the Sponsor. The criteria for repeat analysis, as defined in the respective in-house procedure, will be followed.

[redacted]

7.2.5. Volume of Blood to be Drawn from Each Patient

During this study it is expected that blood will be taken from all patients, regardless of sex. Exact blood volumes to be drawn can be found in the study lab manual. Estimated maximum allowable total blood draw (including plasma PK draws) is no more than 500 mL over 56 days.

7.2.6. Other Tests

[redacted]

7.2.7. Samples and Data for Future Research

Future findings may make it desirable to use the samples and data acquired in this study for future research not described in this protocol. Therefore, all participants in countries where this is allowed will be asked to give a specific consent to allow the Sponsor or a contracted partner to use the samples and collected data for future research. This will be optional for all study patients. Future research and use of data will be subject to prior IEC/IRB approval if required per local legislation.

8. ASSESSMENT OF ADVERSE EVENTS

8.1. Adverse Event Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product, which does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product. This includes any newly occurring event or previous condition that has increased in severity or frequency since starting active or randomized treatment.

A **Serious Adverse Event (SAE)** is any AE occurring at any dose and regardless of causality that:

- results in death
- is life-threatening, (*Note:* The term 'life-threatening' in the definition of 'serious' refers to an event/reaction in which the participant was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death, if it were more severe)
- requires inpatient hospitalization or prolongation of an existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry, are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned)

  Note: The prolongation of hospitalization criterion is based on best clinical judgment of the PI. For the purposes of this study, duration of intended hospitalization at the time of study randomization may be reasonably presumed to be approximately 10 days, as this is the maximum allowed duration of study treatment. Therefore, cases of clinical failure leading to prolongation of hospitalization beyond approximately 10 days should be evaluated for the potential of meeting SAE criteria. The Medical Monitor should be contacted if help is needed in determining reportability of a potential SAE.
- results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions
- is a congenital anomaly/birth defect
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive

treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

In this study, progression or worsening of the index infection (cUTI/AP) is captured as an efficacy outcome (clinical failure) rather than as an AE. However, if clinical failure or complications of the index cUTI/AP meets any of the above seriousness criteria, the event **must** be reported as a SAE. Examples include: clinical failure leading to death, prolongation of hospitalization, or life-threatening complications (e.g., septic shock).

Clarification should be made between the terms "serious" and "severe" since the terms are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours' duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is an SAE that is reported as related to study treatment and is unexpected. The assessment of the expectedness is done by the Sponsor as per applicable regulations. Both expectedness and causality assessment drive the decision for the sponsor to report the SUSAR to Health Authorities and other entities. An AE is considered "unexpected" if it is not listed in the Reference Safety Information (RSI) section of the Investigational Brochure. All SAEs, independently of the expectedness, need to be reported by the site to the Sponsor as described in Section 8.6.

Abnormal Lab findings (e.g., clinical chemistry, hematology, coagulation, and urinalysis) or other abnormal assessments (e.g., ECG parameters, vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions stated above. CS abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at Baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. The Investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is CS.

8.2. Evaluating Adverse Events and Serious Adverse Events

8.2.1. Assessment of Intensity and Outcome

The PI will assess intensity for each AE and SAE reported during the study. The assessment will be based on the PI's clinical judgment using the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Version 5.0) as a guideline, wherever possible. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

- **Mild:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe
- **Life-Threatening or Disabling:** An event that poses an immediate risk of death from the reaction as it occurred
- **Death:** The event resulted in death

The following terms and definitions are used in assessing the final outcome of an AE:

- **Recovered/Resolved:** The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the patient signed the informed consent
- **Recovering/Resolving:** This term is only applicable if the patient has completed the trial or has died from another AE. The condition is improving and the patient is expected to recover from the event
- **Recovered/Resolved with sequelae:** The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure; If a sequela meets an SAE criterion, the AE must be reported as an SAE
- **Not Recovered/Not Resolved:** The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting
- **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as “recovered/resolved”, “recovering/resolving”, “recovered/resolved with sequelae” or “not recovered/not resolved”. An AE with fatal outcome must be reported as an SAE
- **Unknown:** This term is only applicable if the patient is lost to follow-up.

8.2.2. Assessment of Causality

The Investigator is obligated to assess the relationship between the study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment, will be considered and investigated. The Investigator will also consult the IB and/or Product Information for marketed products, in their assessment. For each AE/SAE, the Investigator must document in the medical notes that they have reviewed the AE/SAE and provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment and rationale for the change. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Sponsor will also provide a separate causality assessment of the event, in addition to the Investigator's causality. The combination of the Sponsor and Investigator causalities will drive the reportability of the AE report to Health Authorities and other entities according to the applicable regulations.

The causal relationship between the study treatment and the AE will be assessed according to the following 4-point scale:

- **Unrelated:** clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible, or probable
- **Unlikely:** does not follow a reasonable temporal sequence from administration; may have been produced by the patient's clinical state or by environmental factors or other therapies administered
- **Possible:** follows a reasonable temporal sequence from administration; may have been produced by the patient's clinical state or by environmental factors or other therapies administered
- **Probable:** clear temporal association with improvement on cessation of study drug or reduction in dose; reappears upon re-challenge or follows a known pattern of response to the study drug.

8.2.3. Adverse Events of Special Interest

Previous studies of TBP-PI-HBr did not identify any specific adverse events of special interest (AESI). However, medically important safety topics based on the known class effect for other carbapenem antibiotics and/or the β-lactam class (e.g., hypersensitivity, *C. difficile* infection, hematologic disorders representing low blood counts, etc.), or based on safety topics that are known to result in severe complications for any drug (e.g., liver disorders and/or drug-induced liver injury) will be reviewed.

Further details regarding the search strategy and analysis of potential AESIs will be outlined in the SAP.

8.3. Time Period, Frequency and Method of Detecting AEs

All AEs, including SAEs, will be collected from the time of first study treatment dosing until the LFU visit. As a consistent method of soliciting AEs, the participant shall be asked a non-leading question such as: "How do you feel?"

Any pre-existing conditions or signs and/or symptoms present in a participant prior to the start of the study (e.g., before informed consent) should be recorded as Medical/Surgical History. In addition, any change in health status, which is reported after informed consent, is obtained but prior to receipt of study treatment will be documented as Medical/Surgical History.

Any medical occurrence reported or observed after the first dose of study treatment will be recorded as an AE. AEs will be evaluated by the PI (or designee) and recorded.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent assessments as necessary. If these have been resolved, this should be documented.

8.4. Adverse Event Management

The PI (or designee) will provide appropriate medical care for the clinical management of any AEs related to study participation, whether identified during or after the course of study participation. Evaluation and treatment of any AE (or CS laboratory abnormality) is at the discretion of the Investigator based on their clinical judgment. The applied measures should be recorded in the patient source documents and entered into the CRF as applicable. Referral or collaborative care will be organized if considered necessary by the Investigator. As noted in Section 8.7, the Sponsor may request additional supplemental investigations as needed to elucidate the nature and/or causality of an SAE.

SAEs will be reported to competent authorities by the Sponsor (or delegate) in accordance with national requirements.

8.5. Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the PI (or designee) to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The PI (or designee) will then record all relevant information regarding an AE/SAE in the CRF. It is not acceptable for the PI (or designee) to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the appropriate AE/SAE CRF pages. However, there may be instances when the Sponsor requests copies of medical records for certain cases. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the Sponsor.

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

8.6. SAE Reporting

8.6.1. Regulatory Reporting Requirements for Reporting of SAEs

The PI (or designee) will promptly (within 24 h) report all SAEs to the Sponsor (or delegate). Prompt notification of SAEs by the PI (or designee) to the appropriate Sponsor (or delegate) contact for SAE receipt **is essential** so that the Sponsor may comply with its regulatory obligations. SAEs will be reported to competent authorities in accordance with national

requirements (refer to emergency contact information page at beginning of protocol). For Death and Life-Threatening SUSARs, the timelines for the Sponsor to report to the Health Authorities are 7 calendar days from receipt of the initial information from the PI and a follow-up within 8 calendar days. For all other SUSARs, the timeline for the Sponsor to report to Regulatory Authorities is 15 calendar days from the receipt of the information from the PI.

The PI (or designee) is responsible for notifying the local Institutional Review Board (IRB), local Independent Ethics Committee (IEC), or the relevant local RA of all SAEs that occur at his or her site as required.

8.6.2. Completion and Transmission of the SAE Reports

Once the PI (or designee) becomes aware that an SAE has occurred in a study patient, he/she will report the information to the Sponsor (or delegate) within 24 h. The SAE form (and CRF) will always be completed as thoroughly as possible with all available details of the event, signed by the PI (or designee), and forwarded to the Sponsor (or delegate) and Medical Monitor within the 24 h of the SAE identification. If the PI does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Sponsor (or delegate) and Medical Monitor of the event and completing the form. The form will be updated as soon as possible when additional information becomes available.

The PI will always provide an assessment of causality at the time of the initial report. If no causality is provided, the Sponsor will handle the AE as related for regulatory reporting purposes until clarification is obtained from the PI.

Facsimile transmission or e-mail of scanned copy of the SAE form is the preferred method to transmit this information to the Sponsor (or delegate) and Medical Monitor for SAE receipt. In rare circumstances and in the absence of facsimile, computer and scanner equipment, notification by telephone is acceptable, with a copy of the SAE form sent by overnight mail. Initial notification via the telephone does not replace the need for the PI (or designee) to complete and sign the SAE form within the outlined time frames.

Any event that in the opinion of the PI (or designee) may be of immediate or potential concern for the participant's health or well-being will be reported to the Sponsor Medical Monitor (or delegate).

AEs will be classified as SUSARs if the SAE is assessed as related and meets the definition of "unexpected" in Section 8.1. SUSARs should be reported to the Ethics Committees (ECs) and to the RAs in accordance with applicable regulatory requirements for expedited reporting. It is the Investigator's responsibility to report SUSARs to the ECs. Sponsor or designee is responsible for notifying the relevant RAs (including the authorities in the EEA via EudraVigilance and the IRBs/IECs) and the investigative sites within the specified timeframes of all SUSARs, as applicable per local requirements.

8.6.3. Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside of the nominal AE/SAE study detection period.

Investigators are not obligated to actively seek AE/SAE in former study patients. However, if the PI (or designee) learns of any SAE, including a death, at any time after a participant has completed the study and he/she considers the event reasonably related to the study treatment, the Investigator would promptly notify the Sponsor.

8.7. Follow-up of AEs and SAEs

After the initial AE/SAE report, the PI (or designee) is required to proactively follow each patient and provide further information to the Sponsor on the patient's condition. SAE follow--up should be sent to the Sponsor (or delegate) and Medical Monitor within 24 h using the same timelines and process as described in Section 8.6.2.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing and will be reviewed at subsequent visits/contacts. All AEs must be followed until the patient has recovered/resolved and all queries have been resolved, or until deemed medically stable by the PI (or designee). For cases of chronic conditions or if the patient dies from another event, follow-up until the outcome category is "recovered/resolved" is not required, as these cases can be closed with an outcome of "recovering/resolving" or "not recovered/not resolved".

All patients with SAEs will be followed until they have recovered/resolved, recovered/resolved with sequelae or the event was fatal or until all queries have been resolved, or until the participant is lost to follow-up. Once resolved, the appropriate SAE CRF page(s) will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the PI perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the SAE. If a participant dies during participation in the study or during a recognized follow-up period, the Sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE form and the CRF, with all changes signed and dated by the PI. The updated SAE form should be sent to the Sponsor using the same timelines and process as described in Section 8.6.2.

8.8. Pregnancy

Any report of pregnancy for any female study patient or male study patient's partner must be reported within 1 business day to the Sponsor using the designated pregnancy form. The female study participant must be withdrawn from the study.

A urine or serum β-HCG pregnancy test (according to local SOC) is performed by the local laboratory on all FOCP at the Screening visit and if pregnancy is suspected at any time.

In addition, a serum β-HCG pregnancy test is performed by the central laboratory on all FOCP at the Screening visit and at the patient's final visit (LFU visit or time of early withdrawal from the study) (refer to SOA, Appendix 2).

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30-calendar days post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to the Sponsor (or designee) and the Medical Monitor.

Note: An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.9. Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE. *Note:* The one business day reporting requirement for SAEs also applies to reports of abuse, misuse, overdose, or medication errors.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse:** Persistent or sporadic intentional intake of study treatment when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Medication Error**: An error made in prescribing, dispensing, administration, and/or use of study treatment (For studies, medication errors are reportable to the Sponsor)
- **Misuse:** Intentional use of the study treatment other than as directed or indicated at any dose (*Note:* this includes a situation where the study treatment is not used as directed at the dose prescribed by the protocol)
- **Overdose:** Intentional or unintentional intake of a dose of the study treatment exceeding a pre-specified total daily dose of the product as per protocol.

Cases of patients missing doses of product are not considered reportable as medication errors. Minor dosing errors (i.e., within 20% of correct dose), such as failure to change dosing with small changes in estimated Creatinine Clearance, should not be reported as medication errors and should be captured as protocol deviations.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is always reportable as a medication error. The administration and/or use of an expired product should be considered as a reportable medication error.

Infusion errors related to rate of administration, reconstitution and/or dilution of study treatment, including use of appropriate diluent and the timeframe in which the study treatment is to be used after reconstitution and/or dilution, are reportable as medication errors.

Intentional overdosing of the study treatment is unlikely. In the event of overdose in general, treatment should be supportive and symptomatic according to the patient's clinical presentation.

8.10. Serious Adverse Event Procedures

8.10.1. Reference Safety Information

The reference safety information for this study is the IB, which the Sponsor is providing separately to all Investigators.

The reference safety information for the comparator in this study is the imipenem-cilastatin SmPC (PRIMAXIN I.V. SmPC)/USPI (PRIMAXIN I.V. USPI), which the Sponsor is providing separately to all investigators.

8.10.2. Regulatory Agency, Institutional Review Board, Independent Ethics Committee, and Site Reporting

The Investigator is responsible for notifying the local IRB or local IEC of all SAEs that occur at his or her site as required. The Sponsor or delegate is responsible for reporting to the relevant local RA as required.

9. DATA MANAGEMENT

9.1. Data Collection

The Investigators' authorized site personnel must enter the information required by the protocol on the CRF. Study Monitors (blinded and unblinded) will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Qualified site personnel will address discrepancies between source data and data entered on the CRF. When a data discrepancy warrants correction, authorized site personnel will make the correction. Data collection procedures will be discussed with the site at the site initiation visit and/or at the Investigator's Meeting.

9.2. Clinical Data Management

Data are to be entered into a clinical database as specified in the Data Management Plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

10. STATISTICAL ANALYSES

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study. If, after the study has begun, changes are made to the primary endpoint of the study, the protocol will be amended. If the statistical methods related to those primary hypotheses are amended, this will either be documented via a protocol amendment or explicitly stated in the Statistical Analysis Plan (SAP).

All continuous variables will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using the number of observations and percentages for each category. Percentages will be based on non-missing data unless otherwise specified.

Details of the handling of missing data for the primary efficacy endpoint are given in Section 10.8.2 all other details of handling missing data will be provided in the SAP.

Except where indicated in the SAP, Baseline is defined as the most recent value prior to the start of treatment with the study treatment.

All statistical analyses will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC 27513, USA). The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

10.1. Planned Interim Analysis, Independent Data Monitoring Committee

One IA is planned to assess both efficacy and futility by the IDMC. The IDMC will meet when approximately 60% of patients in the micro-ITT Population have achieved the TOC Visit to evaluate the primary endpoint, identify potential treatment benefit, review safety data, and make recommendations for continuing or stopping the study, as per the IDMC charter. The IDMC can also be convened on an ad hoc basis if the blinded study team identifies a potential safety signal and escalates this to the IDMC to review unblinded data for further evaluation. The IDMC members will include at least five independent experts, including an infectious disease clinician, a chairperson with experience chairing IDMC meetings, a clinical microbiologist, and a statistician with infectious disease experience. Details regarding the IDMC process will be described in the IDMC charter.

An independent unblinded statistical team will conduct and provide all unblinded analyses to the IDMC before the meeting is held. Details on the content and structure of the data output will be described in a separate IDMC analysis plan. Study team members from the Sponsor and CRO that are operating the study and conducting the final analysis will remain blinded. The IDMC and independent team will maintain unblinded data in a secure area to ensure the integrity of the data until the study is completed. Details on protecting blind and data integrity will be described in a blinding plan.

An IA with stopping rules for both efficacy and futility will be performed. The nominal significance levels for the interim and final analyses will be determined using Rho family error spending boundaries (Jennison 2000). The stopping boundary for assessing efficacy at interim will use rho=2 and a (non-binding) stopping rule for futility at interim will use rho=3. The

futility bounds of this study are nonbinding and are considered guidance rather than strict bounds.

During IA, if efficacy success (i.e., non-inferiority [NI]) is reached, one-sided p-value for response rate difference between the two treatment groups will be calculated using the same method to compare against the p-value boundary for superiority.

During the IA, the accrual of the study will continue. If efficacy success (i.e., NI) is reached at the IA and the study is stopped early, the IA will be the primary analysis and data collected between the IA data cut and the time when the study is stopped will be considered overrun. Overrun data will be pooled with the IA data to repeat the primary efficacy analysis as sensitivity analysis. If efficacy success is not reached as assessed by the IDMC at the IA and there are no reasons to stop the study early based on safety concern(s) or futility, the study may continue to the maximum target sample size for the micro-ITT population of approximately 1588 patients.

Details for the IA are described in the IDMC charter.

The Sponsor will review the blinded safety data of this study at regular intervals. Details regarding the safety review process will be available in relevant safety review documents. The safety review group will inform the IDMC if any safety signals are identified.

10.2. Sample Size Determination

10.2.1. Justification of Sample Size

Patients will be randomized to TBP-PI-HBr and imipenem-cilastatin in a 1:1 ratio. Assuming a 60% overall response rate for imipenem-cilastatin and 58% overall response rate for TBP-PI-HBr, a sample size of approximately 1588 patients in the micro-ITT Population is required, for a design with one IA allowing for stopping the study based on efficacy or futility, to provide 89% power to demonstrate NI in the overall response rate of TBP-PI-HBr and imipenem-cilastatin with a 0.025 one-sided alpha level and a -10.0% NI margin. The minimal response rate difference that is estimated to meet the statistical criterion for NI is provided in Table 5.

Table 5: Estimated Minimal Response Rate Difference for Efficacy and Futility Interim Analysis

Design	Information Fraction	micro-ITT Sample Size	Estimated Minimal Response Rate Difference for Non-inferiority
Analysis for Efficacy and Futility	60%	954	-2.5%
	100%	1588	-5.0%

micro-ITT, microbiological Intent-to-Treat.

The study is planned to enroll approximately 2648 patients (1324 per treatment group) to ensure a sufficient number of patients in the primary analysis population (micro-ITT Population) assuming a 60% evaluability rate. The final number of randomized patients may vary based on the evaluability rate for the micro-ITT Population. Response rates of 60% and 58% are assumed for IV imipenem-cilastatin and oral TBP-PI-HBr, respectively.

If the study proceeds after an efficacy and futility IA, the maximum target sample size (assuming there is a decision to continue the study at the IA) for the primary analysis population (micro-ITT Population) will be around 1588 patients (794 patients per treatment group).

10.2.2. Sample Size Sensitivity

Sensitivity of the sample size has been explored considering various overall response rates. Table 6 and Table 7 display the minimum power under various assumptions of "true" therapeutic success rates of TBP-PI-HBr and imipenem-cilastatin under different IA designs, when the IA is conducted at approximately 60% information fraction of the design allowing for efficacy and futility stop at the IA. For all of these cases, the 1-sided type I error is 0.025, the NI margin is -10.0% is used.

Table 6: Power of the Study Under Various Assumptions of the True Therapeutic Success Rates for Efficacy and Futility Group Sequential Design

Therapeutic Success Rate of Imipenem-cilastatin	Therapeutic Success Rate of TBP-PI-HBr	Total Number of Patients in the Primary Analysis	Number of Patients in the Primary Analysis in the Interim Analysis[a]	Power
60%	60%	1588	954	97.8%
60%	59%	1588	954	94.6%
60%	58%	1588	954	88.6%
59%	60%	1588	954	99.2%
59%	59%	1588	954	97.7%
59%	58%	1588	954	94.5%
58%	60%	1588	954	99.7%
58%	59%	1588	954	99.2%
58%	58%	1588	954	97.7%

[a] Number of Patients are rounded up to even numbers.

Table 7: Impact of Evaluability Rate on ITT Population

Therapeutic Success Rate of Imipenem-cilastatin	Therapeutic Success Rate of TBP-PI-HBr	Evaluability Rate	Total Number of Patients in the ITT	Total Number of Patients in the micro-ITT
60%	58%	70%	2270	1588
60%	58%	60%	2648	1588
60%	58%	50%	3176	1588
60%	58%	45%	3530	1588

ITT, Intent-to-Treat; micro-ITT, microbiological Intent-to-Treat; TBP-PI-HBr, tebipenem pivoxil hydrobromide.

10.3. Analysis Populations

Analysis populations are defined below. Please refer to the SAP for additional details.

Intent-to-Treat (ITT) Population: All patients who were randomized, regardless of whether they received any IP or comparator. Patients will be summarized by the treatment to which they were randomized.

Safety Population: Randomized patients who received any amount of IP or comparator. Patients will be summarized by the treatment which they received.

Microbiological Intent-to-Treat (micro-ITT) Population: All randomized patients who have all of the following:

- a baseline urine culture demonstrating $\geq 10^5$ CFU/mL of an Enterobacterales uropathogen (or the same Enterobacterales pathogen is present concurrently in blood cultures and in urine) against which imipenem has antibacterial activity
- no additional pathogens other than an additional Enterobacterales species, *E. faecalis, S. aureus, or S. saprophyticus* are identified in the baseline urine culture at $\geq 10^5$ CFU/mL (or the same pathogen is present concurrently in blood cultures and in urine). In addition, where *E. faecalis, S. aureus, or S. saprophyticus* are identified, imipenem must have antibacterial activity
- no more than 2 microorganisms identified in the baseline urine culture, regardless of colony count.

Note: For Enterobacterales, antimicrobial activity for imipenem is defined as Susceptible according to CLSI Criteria (MIC ≤1 µg/mL); CLSI 2023. For *E. faecalis,* antimicrobial activity will be presumed where the ampicillin MIC is ≤8 µg/mL.
For *S. aureus,* antimicrobial activity will be presumed where the oxacillin MIC is ≤2 µg/mL. For *S. saprophyticus,* antimicrobial activity will be presumed where the oxacillin MIC is ≤0.5 µg/mL.

Clinically Evaluable (CE) Population: Patients who meet the definition for the ITT Population, have no important protocol deviations that would affect the assessment of efficacy including, but

not limited to, a minimum duration of study treatment and treatment compliance ≥80% of expected number of doses (additional deviations as further defined in the SAP), and had an outcome assessed as clinical cure or clinical failure at EOT, TOC, and/or LFU visits, respectively.

Microbiologically Evaluable (ME) Population: Patients who meet the definitions of both the micro-ITT Population and CE Population. In addition, to be included in the ME Population, patients must not have a microbiological outcome of indeterminate.

Note: The ME and CE Populations will be defined for each respective visit (e.g., ME-EOT, ME-TOC, and ME-LFU).

PK Population: All patients treated with at least one relevant dose of TBP-PI-HBr with at least one quantifiable plasma or [redacted] sample according to the subpopulations outlined below:

- **Intensive Plasma PK Subgroup**: approximately 20 TBP-PI-HBr-treated patients with at least one quantifiable plasma PK sample
- **Sparse Plasma PK Subgroup**: all remaining TBP-PI-HBr-treated patients with at least one quantifiable plasma PK sample
- [redacted].

Gram-positive Population: All patients in the ITT population with a baseline urine culture demonstrating ≥10^5 CFU/mL of *E. faecalis, S. aureus,* and/or *S. saprophyticus* (or the same pathogen is present concurrently in blood cultures and in urine) against which imipenem has antibacterial activity AND no more than 2 microorganisms are identified in the urine culture regardless of colony count. Additionally, if a patient has more than 1 pathogen identified, the second pathogen must be *E. faecalis, S. aureus, S. saprophyticus*, or an Enterobacterales spp. This population will be used for supplemental analysis of the treatment effect for these Gram-positive pathogens and will be described in the SAP.

10.4. Patient Disposition

Patients in each analysis population, as well as patients who complete the study and/or treatment, and patients who prematurely discontinue from the study and/or treatment will be summarized by treatment group using descriptive statistics. In addition, for patients who prematurely discontinue from the study and/or treatment, the reasons for discontinuation will be summarized by treatment group. All patients enrolled in the study will be accounted for in the summation.

10.5. Demographic and Baseline Characteristics

Demographic and Baseline disease characteristic data will be summarized for each treatment with frequency distributions and/or descriptive statistics. Descriptive summaries of demographic and Baseline characteristics will be presented by treatment group and overall for the micro-ITT and Safety Populations. Demographic and Baseline disease characteristic data will also be listed.

10.6. Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODRUG/2006QA or newer version).

Any patient record of prior treatment must be documented on the appropriate Case Report Form (CRF) page. Concomitant therapy taken between the dates of the first dose of study treatment and the last study visit, inclusive, are to be listed on the appropriate CRF page.

10.7. Investigational Product Exposure

The number of patients receiving TBP-PI-HBr and imipenem-cilastatin, the planned and total doses received, and along with the duration of exposure and compliance, will be summarized by treatment groups in the study for all patients in the Safety Population.

10.8. Efficacy Analyses

10.8.1. General Considerations

Treatment effect to be estimated for primary and secondary estimands are overall response, clinical response, and microbiological response at the designated visits in patients included in micro-ITT. Intercurrent events (ICE) include receiving other systemic antibacterials and treatment discontinuation; a combination of composite strategy and treatment policy strategy will be implemented to account for the 2 ICEs, respectively. The ICE event strategies determine that:

- treatment effects will be estimated regardless of study treatment discontinuation) when the analysis population is the ITT Population or its derivatives; and
- the definition of a successful response or a positive outcome (clinical resolution and microbiological eradication) precludes the use of other systemic antibacterials prior to the assessment.

Any supplemental analyses will be detailed in the SAP.

10.8.2. Handling of Missing Data

Missing data will be treated as failures for efficacy endpoints as defined in Section 7.2.1. Detailed handling of missing data for other safety endpoints will be presented in the SAP.

10.8.3. Primary Efficacy Endpoint

The primary treatment effect to be estimated (estimand) is overall response (combined clinical cure plus microbiological eradication, defined below) at the TOC visit in the micro-ITT Population. The primary treatment effect will be estimated regardless of treatment discontinuation, as per the treatment policy strategy. The ICE of use of non-study potentially effective systemic antibacterial therapy for the treatment of the index infection (cUTI/AP) is captured through the definitions of microbiological and clinical response and will be counted as failures (composite strategy). If a participant experiences both ICEs of study treatment discontinuation and use of potentially effective systemic antibacterials, then a composite strategy

(assigning overall response as a failure) will be used from the point that the relevant systemic antibacterial was taken. Further details on the primary estimand are provided in Section 3.1.1.

The study is designed to determine whether TBP-PI-HBr, administered PO is non-inferior compared to intravenously administered imipenem-cilastatin with respect to the primary efficacy endpoint of overall response (defined in Section 3.1) at the TOC Visit in the micro-ITT Population.

For the overall response, patients will be categorized as a responder (clinical cure plus microbiological eradication), non-responder (clinical cure only, microbiological eradication only, or neither), or indeterminate response (indeterminate clinical response or indeterminate microbiological response, or both) at TOC. Patients with missing data at TOC, or who are lost to follow-up, will be defined as indeterminate for the primary analysis and will be included in the denominator for the calculation of overall response rate. Thus, patients with an indeterminate outcome will be considered failures for the primary analysis. The number and percentage of patients in each treatment group in each response category at TOC will be reported.

The null and alternative hypothesis are the following:

$H0: P1-P2 \leq -\Delta$

$H1: P1-P2 > -\Delta$

Where:

P1=overall responder (success) rate in the TBP-PI-HBr group,

P2=overall responder (success) rate in the imipenem-cilastatin group,

Δ=10% the NI margin

The population-level effect will be estimated by the difference in percentage response and its 95% CI.

The number and percentage of participants with overall success will be summarized, along with the 95% CI, at the TOC visit by treatment group.

At the IA, if the Z statistic (for the primary analysis population [micro-ITT Population]) is higher than the Z statistic boundary for NI, the study will be stopped for efficacy and NI will be declared.

At the final analysis (if the study continues at the IA), if the Z statistic (for the primary analysis population [micro-ITT Population]) is higher than the Z statistic boundary for NI the study will be declared successful and NI will be declared. Refer to Section 7.2.1 for further details on study success definition and Section 10.1 for IA recommendation framework.

If NI is declared between TBP-PI-HBr and imipenem-cilastatin, superiority will be tested in the primary analysis population (micro-ITT Population) with the following null and alternative hypotheses:

$H0: P1-P2 \leq 0$

$H1: P1-P2 > 0$

Where:

P1=overall responder (success) rate in the TBP-PI-HBr group,

P2=overall responder (success) rate in the imipenem-cilastatin group,

If the one-sided p-value is less than the p-value boundary superiority of TBP-PI-HBr will be declared.

The difference in therapeutic success rates between the two study treatment groups and its Z statistic use the Miettinen-Nurminen method (Miettinen 1985) stratified by age at informed consent (≥18 to <65 years vs. ≥65 years), baseline diagnosis (AP vs. cUTI), and presence or absence of urinary tract instrumentation at Baseline.

In the event that any patients are mis-stratified, for the primary efficacy analysis, the actual diagnosis, age and urinary tract instrumentation collected in eCRF will be used to create actual pooled stratification.

A sensitivity analysis of the primary efficacy analysis will also be conducted from the pooled stratification as randomized. Additional sensitivity analysis may be performed, details will be provided in the SAP.

Subgroup analysis and supplemental analysis on additional populations (e.g., Gram-positive Population) for the primary endpoint may be performed with details provided in the SAP.

Handling of protocol deviations will be described in the SAP.

The primary efficacy data will be listed for the micro-ITT Population. In addition, a sensitivity analysis of the primary endpoint will be performed for the CE Population to assess general consistency with the primary analysis.

10.8.4. Secondary Efficacy Analyses

Secondary efficacy endpoints (refer to Section 3.1) for clinical response will be summarized using the micro-ITT, CE and ME Populations as applicable. Secondary efficacy endpoints for microbiological response, as well as overall response, will be summarized using the micro-ITT and ME Populations. There will be no multiplicity adjustment for the testing of the secondary endpoints. No formal hypothesis testing will be performed. For the list of secondary endpoints refer to Section 3.1 and definitions in Section 7.2.1.

Supplemental analysis on additional populations (e.g., Gram-positive Population) for the secondary endpoints may be performed with details provided in the SAP.

[redacted]

10.9. Safety Analyses

All safety analyses will be summarized and listed using the Safety Population. Primary assessments of safety will include assessments of treatment-emergent adverse events (TEAEs),

clinical laboratory (hematology, clinical chemistry, and urinalysis) changes, ECGs, and vital sign changes.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. AEs will be recorded from the first dose of study treatment through LFU. TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of study treatment through LFU.

The number of events, incidence, and percentage of TEAEs will be summarized by treatment group and overall, and by system organ class and preferred term. TEAEs will also be summarized by severity, relationship to study treatment leading to withdrawal, SAEs, and deaths. These AEs will also be listed. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same patient more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to study treatment.

Clinical laboratory tests, vital signs, and ECG findings will be summarized by treatment group and overall using descriptive statistics for the actual value at each time point.

Change from Baseline will be calculated for vital signs and selected clinical laboratory tests WBC count, Hgb, liver function tests [AST, ALT, ALP], BUN, serum Cr, and estimated CrCl [based on Cockcroft-Gault formula]) at each time point by treatment group. Shift tables of the worst on-study laboratory toxicity based on CTCAE v 5.0 grading relative to Baseline will be presented by treatment group for these selected clinical laboratory tests. Plots of laboratory values versus time for key laboratory parameters may also be provided.

Abnormal physical examination results will be recorded as part of the medical history (if at Screening) or will be captured as AEs (when appropriate on-study); therefore, physical exam data will not be summarized in a table. All safety data will also be listed.

10.10. Other Analyses

10.10.1. Pharmacokinetic Analyses

TBP plasma concentration-time data from TBP-PI-HBr treated (Treatment Group 1) patients will be used to characterize the PK of TBP in the target population using PK modeling, to be separately reported. Concentration values will be listed by patient and actual time after dose.

[redacted]

11. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is to be conducted in accordance with the protocol and current applicable RA guidelines, International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) Guidance (FDA 2018a), European Union (EU) Clinical Trials (CT) Regulation 536/2014 (European Commission 2014) and its updates, and local ethical and legal requirements.

11.1. Sponsor's Responsibilities

11.1.1. Good Clinical Practice Compliance

The study start date is the date on which the clinical study will be open for recruitment of participants (i.e., when the first site is open). The study Sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations and ICH E6(R2) GCP Guidance (FDA 2018a) and EU CT Regulation 536/2014 (European Commission 2014).

Representatives of the study Sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, patients' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines conduct visits to sites. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor ensures that local RA requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any RA approvals required prior to release of study treatment for shipment to the site.

The sponsor will notify the authorities as applicable (in line with country/region requirements) about a serious breach of the regulations or of the version of the protocol applicable at the time of the breach. A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the CT.

11.1.2. Indemnity/Liability and Insurance

The Sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the CRO/Investigator as necessary.

11.1.3. Public Posting of Study Information

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating Investigators' names and contact information.

11.1.4. Submission of Summary of Clinical Study Report to Regulatory Agencies and Independent Ethics Committees

The Sponsor will provide a Clinical Study Report (or its summary) within one year of the end of the study completion date to the agencies, and IECs, as applicable, in line with country requirements.

For the EU countries: irrespective of the outcome of the CT, the Sponsor will submit a summary of the intermediate results of the clinical study to the relevant EU clinical study database (the CT Information System database at https://euclinicaltrials.eu/home) in a timely manner. As appropriate, the final study results posting this will be accompanied by a summary written in a manner that is understandable to laypersons.

11.1.5. Study Suspension, Termination, and Completion

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable regulatory agencies and IRBs/IECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study, which has been posted to a designated public website, will be updated accordingly.

Reasons for terminating the study may include but are not limited to:

- if efficacy success (NI) is reached at the IA
- the discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- failure to enroll patients at an acceptable rate
- a decision on the part of the Sponsor to suspend or discontinue development of the IP
- regulatory agency decision.

Notification of the end of study will be done in accordance with EU CT Regulation 536/2014. End of study is the time at which all required data has been collected to answer the research question(s) in the protocol.

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6(R2) (1996), EU CT Regulation 536/2014, and applicable regulatory requirements and guidelines.

It is the Investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable patients within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. Curriculum vitae for Investigators and sub-Investigators will be provided to the study Sponsor (or designee) before starting the study.

If a potential research patient has a primary care physician, the Investigator should, with the patient's consent, inform them of the patient's participation in the study.

11.2.2. Protocol Adherence and Investigator Agreement

The Investigator and any co-Investigators must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those patients who have met protocol eligibility criteria. Investigators are required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

If the Investigator suspends or terminates the study at their site, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The Investigator will also return all drug product, containers, and other study materials to the Sponsor. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by national or regional regulations.

Communication with local IRBs/IECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the Sponsor, CRO, Investigator, or for multi-site studies, the Coordinating PI according to national provisions and will be documented in the Investigator Agreement.

11.2.3. Documentation and Retention of Records

11.2.3.1. Microbiological Reports

Microbiological reports will be retained according to applicable laws and regulations.

11.2.3.2. Case Report Forms

Electronic Case Report Forms (eCRFs) and CRFs will be handled in accordance with instructions from the Sponsor.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded to CRFs/eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. The Investigator or designee as stated in the site delegation log must complete eCRFs.

11.2.3.3. Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but is not limited to patient's medical file, original clinical laboratory reports, and histology and pathology reports. All key data must be recorded in the patient's medical records. Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical

records must be available. Definition of what constitutes source data can be found in the Monitoring Plan.

Investigators and institutions involved in the CT must permit clinical-trial monitoring and permit authorized representatives of the Sponsor, the respective national, local, or foreign regulatory authorities, the IRB/IEC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The Study Monitor (and auditors, IRB/IEC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the patient agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB/IEC having access to source data (e.g., patient's medical file, appointment books, original laboratory reports, X-rays).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, European Medicines Agency [EMA], or an auditor).

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the Sponsor.

11.2.3.4. Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local RAs), the EMA, other RAs, the Sponsor or its representatives, and the IRB/IEC for each site.

11.2.3.5. Financial Disclosure

Upon submission of a marketing application to the FDA for any drug, the Sponsor must provide the FDA with a list of clinical Investigators who conducted a sponsored clinical study and certify or disclose financial arrangements.

The Investigator is required to disclose any financial arrangement during the study and for one year after, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research; compensation in the form of equipment; retainer for ongoing consultation or honoraria; any proprietary interest in IP; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

In consideration of participation in the study, the Sponsor pays the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

11.2.4. Compliance to all Local, State, and National Infectious Disease Regulations and Legislation

When using substances for infectious diseases, the Investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of such substances.

11.3. Ethical Considerations

11.3.1. Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study patients prior to any study-specific procedures including Screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each patient or the patient's legally-authorized representative is requested to sign the patient Informed Consent Form or a translation, after the patient has received and read (or been read) the written patient information and received an explanation of what the study involves. This includes, but is not limited to the objectives, potential benefits and risk, inconveniences, and the patient's rights and responsibilities. A copy of the informed consent documentation (e.g., a complete set of patient information sheets and fully executed signature pages) must be given to the patient or the legally-authorized representative of the patient. If applicable, a consent form provided in a certified translation of the local language. Signed consent forms must remain in each patient's study file and must be available for verification at any time.

If patients will be included who are incapable of giving informed consent, a justification for including them should be provided.

The PI will provide the Sponsor with a copy of the consent form, which was reviewed by the IRB/IEC and which received their favorable opinion/approval. A copy of the IRB/IEC's written favorable opinion/approval of these documents must be provided to the Sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (e.g., Sponsor or Coordinating PI) is responsible for this action. Additionally, if the IRB/IEC requires modification of the sample patient Information and Consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

11.3.2. Institutional Review Board or Independent Ethics Committee

For sites in the EU, study sponsor or its delegate will perform submissions to the Member States for the study review as defined by the EU CT Regulation 536/2014.

For sites outside the EU, it is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or their designee), relevant supporting information and all types of patient recruitment information to the IRB/IEC for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs/IECs is defined in the Investigator Agreement.

Prior to implementing changes in the study, the Sponsor and the IRB/IEC must approve any revisions of any revised informed consent documents and amendments to the protocol unless there is a patient safety issue.

Drug product supplies will not be released until the Sponsor/CRO has received written IRB/IEC approval of and copies of revised documents.

For sites outside the EU, the Investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and changes made to the protocol, at least once a year. Sites within the EU can receive an update by the Sponsor, the Investigator or, for multi-site studies the Coordinating PI, according to national provisions. The Investigator must also keep the local IRB/IEC informed of any serious and significant AEs.

11.4. Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). A site that is not a Covered Entity as defined by HIPAA must provide documentation of this fact to the CRO/Sponsor.

The General Data Protection Regulation requires that data is not kept as identifiable personal data for longer than is necessary in relation to the purposes for which it is processed. Personal data processed solely for research purposes may be stored for longer periods as long as appropriate safeguards are in place. All data and remaining samples may be used by the Sponsor for 15 years. Use of individual patient data and/or remaining samples may result in patents or have other monetary value. These patents or other products resulting from patient samples/microorganisms/data will be owned by the Sponsor. There will be no financial benefit from future research on patient data and microorganism samples.

The confidentiality of records that may be able to identify patients will be protected in accordance with applicable laws, regulations, and guidelines.

Measures must be described that will be implemented to ensure confidentiality of records containing personal data of patients. In particular, that personnel of the site, sponsor, CRO and any vendors involved in data processing by the Sponsor, are bound by obligations of confidentiality and the patients will be assigned a unique identifier. Any patient records or datasets that are transferred to the Sponsor will contain this unique identifier only; patient names or any information which can re-identify the patient will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. Such information shall be provided as part of the ICF or a stand-alone form added to the ICF. The patient must be informed that his/her medical records containing identifying personal data will be reviewed by the Sponsor monitors and may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The contract between Sponsor and study sites specifies the responsibilities of the parties regarding data protection, including handling of data security breaches and respective communication and cooperation of the parties. The process to handle data security breaches, in

order to mitigate the possible adverse effects of such breaches to the privacy of study patients, must be described.

Organizational and technical arrangements that will be implemented to avoid unauthorized access, disclosure, dissemination, alteration, or loss of personal data processed must be described in study documents. In particular, the information technology systems used to collect, process, and store study-related data are secured through the implementation such as technical and organizational security measures.

11.5. Publication Policy

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor, in advance of submission. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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APPENDIX 1. SECONDARY ESTIMANDS TABLE

Secondary Endpoint	Population(s)	Treatment Condition	Variable	Summary Measure	Intercurrent Event[a]
Overall response at TOC among cUTI/AP patients infected with Enterobacterales uropathogens at Baseline	micro-ITT	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Overall response	Difference in the overall response rate in the TBP- PI-HBr and imipenem-cilastatin treatment groups in the designated subset	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials– composite strategy
Overall response (combined clinical cure plus microbiological eradication) at TOC	ME	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Overall response	Difference in the overall response rate in the TBP- PI-HBr and imipenem-cilastatin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy
Overall response (combined clinical cure plus microbiological eradication) as defined at the EOT, TOC and LFU	micro-ITT	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Overall response	Difference in the overall response rate in the TBP- PI-HBr and imipenem-cilastatin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy
Overall response (combined clinical cure plus microbiological eradication) as defined at the EOT, TOC and LFU	ME	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Overall response	Difference in the overall response rate in the TBP- PI-HBr and imipenem-cilastatin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy

Secondary Endpoint	Population(s)	Treatment Condition	Variable	Summary Measure	Intercurrent Event[a]
Clinical response at EOT, TOC, and LFU	micro-ITT	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Clinical response	Difference in the clinical response rate in the TBP- PI-HBr and imipenem-cilastatin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy
Clinical response at EOT, TOC, and LFU	CE	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Clinical response	Difference in the clinical response rate in the TBP- PI-HBr and imipenem-cilastatin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy
Per-patient and by-pathogen microbiological response rates at EOT, TOC, and LFU	micro-ITT	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Per-patient microbiologic outcome and by-pathogen microbiologic outcome	Difference in the microbiological success rate in the TBP-PI-HBr and imipenem-cilastatin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy
Per-patient and by-pathogen microbiological response rates at EOT, TOC, and LFU	micro-ITT	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Per-patient microbiologic outcome and by-pathogen microbiologic outcome	Difference in the microbiological success rate in the TBP-PI-HBr and imipenem-cilastatin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy

Secondary Endpoint	Population(s)	Treatment Condition	Variable	Summary Measure	Intercurrent Event[a]
Per-patient and by-pathogen microbiological response rates at EOT, TOC, and LFU	ME	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Per-patient microbiologic outcome and by-pathogen microbiologic outcome	Difference in the microbiological success rate in the TBP-PI-HBr and imipenem-cilastatin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy
Overall, clinical and microbiological response rates at EOT, TOC and LFU among patients infected with drug-resistant Enterobacterales uropathogens e.g., extended spectrum β-lactamase (ESBL)-producing, fluoroquinolone-nonsusceptible (FQ-NS), and/or trimethoprim-sulfamethoxazole-resistant (TMP/SMX-R) strains	micro-ITT	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	Overall, clinical and microbiologic response	Difference in the overall, clinical and microbiological response rates in the TBP-PI-HBr and imipenem-cilastatin treatment groups in the designated subset	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – composite strategy
Safety	Safety Population	TBP-PI-HBr 600 mg every 6 hours daily compared with imipenem-cilastatin 500 mg every 6 hours daily for 7-10 days	TEAEs, SAEs, as well as change from Baseline results for clinical laboratory tests, ECGs, and vital sign measurements	Summary statistics (appropriate for each type of endpoint) in the TBP- PI-HBr and imipenem-cilastatin treatment groups separately	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antibacterials – treatment policy

Secondary Endpoint	Population(s)	Treatment Condition	Variable	Summary Measure	Intercurrent Event[a]
TBP concentration data	PK Population	TBP-PI-HBr 600 mg every 6 hours daily for 7-10 days	TBP plasma concentration	Summary statistics	Study treatment discontinuation (due to any reason) – while on treatment strategy

[a] For each of the secondary endpoints the estimand will follow a similar approach to the estimand for the primary endpoint and will use the same general strategies for the ICEs, with necessary adaptations for the ME and CE Population definitions.

CE, clinically evaluable; cUTI, complicated urinary tract infection; ECG, electrocardiogram; EOT, End-of-Treatment; ICE, intercurrent event; LFU, Late Follow-up; MIC, minimum inhibitory concentration; ME microbiologically evaluable; micro-ITT, Microbiological Intent-to-Treat; PK, Pharmacokinetic; SAE, serious adverse event; TBP, tebipenem; TBP-PI-HBr, tebipenem pivoxil hydrobromide; TEAE, treatment-emergent adverse event; TOC, Test-of-Cure.

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APPENDIX 2. SCHEDULE OF ASSESSMENTS

Study Period	**Screening/ Baseline**	**Treatment**			**Follow-Up**	
Visit or Study Day	**-1 or 1**	**Days 1 through 10**			**17 ±2 Days**	**28 ±2 Days**
Study Day	**Screening** [a]	**1 (Post-Rand.)**	**2 – 10**	**EOT** [b]	**TOC** [c]	**LFU** [d]
Informed Consent	X					
Medical & Surgical History [e]	X					
Height and Weight	X					
Physical Examination [f]	C	F	F	C	C	C
Vital Signs (T, P, RR, BP) [g]	X	X	X	X	X	X
Collection of cUTI/ AP Signs and Symptoms	X	X	X	X	X	X
12-Lead ECG [h]	X	X		X		
Local Labs for Eligibility (Safety and Pregnancy Testing) [i]	X					
Local Serum Creatinine to Assess Renal Function for Dose Adjustments [j]	X	X	X			
Central Labs (Blood/Urine for Safety) [k]	X	X	X	X	X	X
[redacted]						
Blood Cultures [m]	X	<----------X---------->				
Study Treatment Administration [n]		X	X			
Blood Sample for Plasma PK [o]			X			
[redacted]						
Investigator Assessment of Clinical Outcome				X	X	X
Prior and Concomitant Therapy	X	X	X	X	X	X
Adverse Events [r]		X	X	X	X	X

a. Screening procedures must be completed within 24 h prior to randomization on Day 1. Screening laboratory assessments for eligibility will be performed at the local/regional laboratory. Standard-of-care assessments performed at the site within the Screening period (within 24 h of randomization) may be used to determine patient eligibility even if performed prior to signing the ICF; however, study-specific assessments such as ECGs, blood cultures (if using a study-specific regional laboratory), and Screening safety labs collected for analysis by the central laboratory, must be performed after signing the ICF (refer to Section 7.1.1 for details). If Screening visit and Day 1 occur on the same calendar day: complete physical exam at Screening is required, while Day 1 focused physical exam is optional; vital signs at Screening are required, while repeated Day 1 vital signs are optional (if repeated vital signs are collected, record the highest daily temperature in the eCRF); assessment of cUTI/AP clinical signs and symptoms at Screening is required, while Day 1 assessment of clinical signs and symptoms is optional; and separate Screening and Day 1 ECGs must be performed (i.e., Day 1 single ECG must be performed 1 h [±15 min] after the first oral dose administration) (refer to Section 7.1.2 for details).

b. Study treatment administration is 7-10 calendar days for all patients. The EOT visit occurs on the calendar day or the day following (+1 day) the last dose of study treatment. All EOT procedures may be performed the day following last dose of study treatment with the exception of the EOT ECGs, which must be performed 1 hour (±15 min) after the last dose rather than the following day. Lab assessments that are required on the day of last dose and EOT do not need to

be duplicated; for instance, if Day 7 and EOT occur on the same day, the EOT central lab assessment kit should be used in place of Day 7 kit.

c. TOC visit: Day 17 ±2 days. The procedures at the TOC visit should be performed for all patients including those who prematurely discontinue study treatment.
d. LFU visit: Day 28 ±2 days. The procedures at the LFU visit should be performed for all patients including those who prematurely discontinue study treatment.
e. Obtain medical/surgical history, including urological history and any active or inactive conditions diagnosed within the previous 5 years.
f. Complete physical examinations (C) at Screening, EOT, TOC, and LFU visits consist of skin, head and neck, heart, lung, abdomen (including suprapubic area), extremities, back/flank/costovertebral angle tenderness, and neuromuscular assessments. Focused physical examinations (F) between Day 1 and EOT visits are symptom-based assessments. If Screening visit and Day 1 occur on the same calendar day the focused physical exam on Day 1 is optional.
g. Vital signs include blood pressure, pulse, respiratory rate, and temperature. Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be collected at Screening, daily Day 1 through EOT (prior to daily IV infusions), TOC, and LFU visits. Body temperature may be taken per the site's preferred method but limited to oral, tympanic, rectal, or core measurements. The same method of measuring a patient's body temperature should be used throughout the study. If Screening visit and Day 1 occur on the same calendar day, repeated vital signs on Day 1 are optional.
h. Single 12-lead ECGs will be performed for assessment of eligibility at the Screening visit. Repeat single 12-lead ECGs will be performed on Day 1 (after the first dose of oral dose administration) and at the EOT visit (after the last dose of oral dose administration) 1 h (±15 min) and as otherwise clinically indicated after oral dose administration.
i. Results from the local blood and urine samples are used to determine eligibility (results can be from samples obtained up to 24 h prior to randomization). Assessments include serum creatinine (for CrCl calculation), ALT, AST, total bilirubin, absolute neutrophil count, blood urea nitrogen (or blood urea), urinalysis (for nitrite, LE and WBC in spun or unspun urine). A urine or serum beta human chorionic gonadotropin (β-HCG) pregnancy test (according to local standard-of-care) is performed by the local laboratory on all FOCP at the Screening visit, and if pregnancy is suspected at any time.
j. Serum creatinine (for CrCl calculation) should be assessed every 3 days for patients with normal renal function at Baseline and at least once daily for patients with moderate renal impairment from the time of first dose until the CrCl stabilizes. If available, weight on the day of the serum creatinine measurement to be used for calculating CrCl.
k. The central safety laboratory will perform the following evaluations on blood and urine samples: hematology, coagulation, blood chemistry (including L-carnitine), and complete urinalysis. Central safety labs during treatment will be performed on Screening, Day 1 (if the Screening central safety labs are collected on Day 1, the Day 1 labs do not need to be repeated), Day 3, Day 5, Day 7, Day 9 (if still receiving study treatment), EOT, TOC, and LFU visits. In addition, serum β-HCG is performed on all FOCP at the Screening visit and at the patient's final visit (LFU visit or time of early withdrawal from the study) by the central laboratory.
l. [redacted]
m. Collect 2 sets of blood cultures (each set is 1 aerobic and 1 anaerobic blood culture bottle for a total of four bottles) from 2 separate venipuncture sites at Screening. Blood cultures should be repeated on the day that a previous (e.g., Baseline) blood culture is determined to be positive (e.g., reveals growth of a uropathogen). Blood cultures should be repeated as necessary until negative blood cultures are obtained.
n. The tebipenem treatment group will be administered tebipenem 2×300 mg film-coated tablets PO for a total of 600 mg q6h (±1 h) plus dummy IV infusion over 30 min q6h (±1 h). The imipenem-cilastatin treatment group will receive imipenem-cilastatin for IV injection, administered as a 500 mg IV infusion over 30 min q6h (±1 h) plus dummy placebo tablets administered PO q6h (±1 h); refer to Figure 1. See Table 3 and Table 4 for dose adjustments in patients with renal impairment.

o. Blood samples using sparse sampling (3 samples/patient) will be collected following any oral dose on Day 2 or Day 3 (fifth, sixth, seventh, or eighth dose) at the following time intervals after oral administration of IP: 1 h (±15 min), 4 h (±0.5 h), and 6 h (±1 h but prior to the next scheduled dose). Blood samples for intensive PK sampling (7 samples per patient) will be collected following oral dosing on Day 2 or Day 3 (fifth, sixth, seventh, or eighth dose) at the time intervals after oral administration of IP: at 15 min (±2 min), 30 min (±5 min), 1 h (±5 min), 1.5 h (±5 min), 2 h (±10 min), 4 h (±10 min), and 6 h (±15 min but prior to the next scheduled dose). The exact dose time and the exact PK sample time should be collected for all patients when collecting PK samples. Intensive PK assessment is optional, patients will need to sign a separate consent.

[redacted]

r. AEs will be collected from the time of the first dose of study treatment.

ALT, alanine transaminase; AP, acute pyelonephritis; AST, aspartate aminotransferase; β-HCG, beta human chorionic gonadotropin; BP, blood pressure; C, complete; CFU, colony forming unit; CrCl, creatinine clearance; cUTI, complicated urinary tract infection; ECG, electrocardiogram; eCRF, electronic case report form; EOT, End-of-Treatment; F, focused; FOCP, females of childbearing potential; GS, Gram stain; h, hour(s); ICF, informed consent form; IP, investigational product; IV, intravenous(ly); LE, leukocyte esterase; LFU, Late Follow-up; min, minute(s); P, pulse; PK, pharmacokinetic; q6h; every 6 hours; PO, orally; Rand, randomization; RR, respiratory rate; T, temperature; TBP, tebipenem; TOC, Test-of-Cure; UC, urine culture; WBC, white blood cells.