Official Title:	**A Phase 3, Randomized, Double-blind, Double-dummy, Multicenter, Prospective Study to Assess the Efficacy, Safety and Pharmacokinetics of Orally Administered Tebipenem Pivoxil Hydrobromide (SPR994) Compared to Intravenous Ertapenem in Patients with Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)**
NCT Number:	NCT03788967
Document Date:	Protocol Version 4.0: 26 May 2020

PROTOCOL TITLE:	**A Phase 3, Randomized, Double-blind, Double-dummy, Multicenter, Prospective Study to Assess the Efficacy, Safety and Pharmacokinetics of Orally Administered Tebipenem Pivoxil Hydrobromide (SPR994) Compared to Intravenous Ertapenem in Patients with Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)**
PROTOCOL NAME:	ADAPT-PO
PROTOCOL NUMBER:	SPR994-301
DRUG:	Tebipenem Pivoxil Hydrobromide 300 mg film-coated tablet (also known as SPR994) and Ertapenem (comparator)
IND:	132744
EUDRACT NO.:	2018-003671-35
SPONSOR:	Spero Therapeutics, Inc. 675 Massachusetts Avenue 14th Floor Cambridge, MA 02139 https://sperotherapeutics.com/
PROTOCOL VERSION AND DATE:	Version 4.0, 26 MAY 2020

GCP Statement: This study will be conducted in compliance with Good Clinical Practice (GCP) guidelines 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.

PROTOCOL SIGNATURE PAGE

Sponsor's Approval: By my signature, I confirm that I have reviewed this protocol and find its content to be acceptable.

Signature:	**Date:**
[redacted]	1 JUNE 2020
[redacted], MD Spero Therapeutics, Inc.	

INVESTIGATORS ACKNOWLEDGEMENT

I have read the ADAPT-PO protocol, numbered SPR994-301, A Phase 3, Randomized, Double-blind, Double-dummy, Multicenter, Prospective Study to Assess the Efficacy, Safety and Pharmacokinetics of Orally Administered Tebipenem Pivoxil Hydrobromide (SPR994) Compared to Intravenous Ertapenem 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 subject 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 Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory 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 Name:	
Site Name:	
Site Number:	

Signature: _____ **Date:** _____
DD-MMM-YYYY

EMERGENCY CONTACT INFORMATION

In the event of a Serious Adverse Event (SAE), the Investigator must fax or e-mail the Clinical Trial Serious Adverse Event Form within one business day to the Safety Desk:

- **E-mail**: [redacted]
- **Pharmacovigilance SAE Fax Number:** Country-specific safety lines will be provided by the Contract Research Organization (CRO), as recorded in the Safety Management Plan.

For protocol- or safety-related issues during normal business hours, the Investigator must contact the Medical Monitor.

- **Sponsor Medical Monitor:**

[redacted], MD
[redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Spero Therapeutics, Inc. 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).

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Origin of Product Quality Complaint	**E-mail Address**
North and South America	[redacted]
European Union (EU) and Rest of World	[redacted]

STUDY SYNOPSIS

Protocol number: SPR994-301	**Investigational Product (IP):** Tebipenem pivoxil hydrobromide 300 mg film-coated tablet (also known as SPR994) and Ertapenem (Comparator)

Protocol Title: A Phase 3, Randomized, Double-blind, Double-dummy, Multicenter, Prospective Study to Assess the Efficacy, Safety and Pharmacokinetics of Orally Administered Tebipenem Pivoxil Hydrobromide (SPR994) Compared to Intravenous Ertapenem in Patients with Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)

Indication: cUTI including AP

Number of Subjects (total and for each treatment arm):

A total of approximately 1,200 subjects, up to a maximum of 1,450 (contingent on a sufficient number of evaluable subjects):

- Tebipenem Pivoxil Hydrobromide (TBPM-PI-HBr) = approximately 600 subjects
- Ertapenem = approximately 600 subjects

Site(s): Approximately 95 sites in Central and Eastern Europe, South Africa and the United States

Study Period (planned): ~Q1 (FPI) 2019 – Q3 (LPO) 2020

Objectives:

Primary:

- To assess the overall response (combined clinical cure plus microbiological eradication) of oral TBPM-PI-HBr compared to intravenous (IV) ertapenem in subjects ≥18 years of age with cUTI/AP
- To assess the safety of oral TBPM-PI-HBr compared to IV ertapenem in subjects ≥18 years of age with cUTI/AP

Secondary:

- To compare clinical cure rates between treatment groups
- To compare microbiological eradication rates between treatment groups
- To assess the population pharmacokinetics (PK) of TBPM-PI-HBr in subjects with cUTI/AP; the dosage of TBPM-PI-HBr will be confirmed based off a blinded analysis of PK data from the first approximately 35 enrolled TBPM-PI-HBr subjects

Exploratory:

- To determine whether treatment with TBPM-PI-HBr or ertapenem is associated with enteric colonization with antibiotic-resistant *Enterobacteriaceae*

- To compare microbiological eradication rates and clinical improvement at Day 5 between treatment groups
- To assess clinical, microbiological, and overall responses in subjects with cUTI/AP caused by ESBL-producing *Enterobacteriaceae*

Rationale:

The key purpose of this study is to evaluate the efficacy, safety and PK of TBPM-PI-HBr compared to IV ertapenem, in subjects with cUTI/AP.

Rationale for Comparator:

Ertapenem was chosen as the comparator for this study because it is approved for the treatment of cUTI/AP in many countries, and is considered an empiric standard-of-care treatment option. Ertapenem has bactericidal activity against primary pathogens that cause cUTI/AP, including extended spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*. Ertapenem is associated with high urinary concentrations, has a similar *in vitro* spectrum of activity, and is in the same antibiotic class (carbapenem) as TBPM-PI-HBr.

Investigational Product, Dose, and Mode of Administration:

- TBPM-PI-HBr 300 mg film-coated tablets, administered orally 600 mg (2 tablets) three times per day (q8h ±0.5 h) plus a single dummy IV infusion over 30 minutes (min) once daily (q24h ± 0.5h); subjects with moderate renal insufficiency (creatinine clearance [CrCl] >30 to ≤50 mL/min) require TBPM-PI-HBr dosage adjustment to 300 mg (1 tablet) q8h ± 0.5 h
- Ertapenem for IV injection, administered as a 1-gram IV infusion over 30 min once daily (q24h ± 0.5h) plus dummy placebo tablets administered orally q8h (±0.5 h)
- Dummy: Normal saline (0.9% sodium chloride) for IV infusion or placebo tablets

Methodology:

This is a Phase 3, randomized, double-blind, double-dummy, multicenter, multinational, prospective study to assess the efficacy, safety and PK of TBPM-PI-HBr administered orally compared to subjects receiving ertapenem administered IV for cUTI/AP.

This study will enroll approximately 1,200 subjects. All subjects will present with a clinical diagnosis of cUTI/AP sufficient to start empiric antibiotics and be able to tolerate oral medication. A dummy infusion of normal saline and dummy placebo tablets will be used to maintain the blind.

Subjects will be randomized (enrolled) to one of two treatment arms at a 1:1 ratio receiving (i) TBPM-PI-HBr or (ii) ertapenem. Randomization will be stratified by:

- Baseline diagnosis (AP vs. cUTI)
- Age at informed consent (≥18 to <65 years vs. ≥65 years)

Subjects who meet the disease definition of cUTI (e.g., underlying functional or anatomical urinary tract abnormality) and have additional clinical evidence of AP (e.g., flank pain or

costovertebral angle tenderness) should be randomized as cUTI. At least 30% of subjects will be randomized with a diagnosis of AP at study entry.

A blinded assessment of evaluability rates and response rates will be performed when 70% of the subjects have response data at Test-of-Cure (TOC) available and will be performed by the blinded Sponsor Data Review Committee. If assumptions are very different from those expected, the sample size may be increased to a maximum of 1,450 subjects.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Male and female subjects at least 18 years of age
2. Able to provide informed consent
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, in order to tolerate oral study drug.
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; fever must be observed and documented by a health care provider (oral, tympanic, rectal or core temperature >38.0°C [>100.4°F])
        ii. Dysuria, urgency to void, or increased urinary frequency
        iii. Nausea or vomiting, as reported by the subject
        iv. Lower abdominal, suprapubic, or pelvic pain

    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 hours 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 milliliter (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 End-of-Treatment [EOT])
        iv. Known intrinsic renal disease with blood urea nitrogen (BUN) >20 mg/deciliter (dL), or blood urea >42.8 mg/dL, or serum creatinine >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; fever must be observed and documented by a health care provider (oral, tympanic, rectal or core temperature >38.0°C [>100.4°F])
ii. Peripheral white blood cell count (WBC) $\geq$10,000/mm^3 or bandemia ($\geq$ 15% immature polymorphonuclear neutrophils [PMNs], regardless of WBC count)
iii. Nausea or vomiting, as reported by the subject
iv. Dysuria, urgency to void, or increased urinary frequency

Note: Subjects who meet the definition for cUTI (Inclusion Criterion 4a) and also 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 hours 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 cubic millimeter (mm^3) in unspun urine
   c. Positive leukocyte esterase (LE) on urinalysis

   Note: Subjects may be randomized and administered IP prior to knowledge of urine culture results.
6. Expectation, in the judgment of the Investigator, that the subject will survive with effective antibiotic 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. Subjects must agree to use a highly-effective method of birth control; male subjects must agree to use an effective barrier method of contraception from Screening through Late Follow-Up (LFU) and for 90 days following the last dose if sexually active with a female of childbearing potential (FOCP); female subjects must not be pregnant or nursing, and must commit to either sexual abstinence or use at least 2 medically accepted, effective methods of birth control (e.g., condom, spermicidal gel, oral contraceptive, indwelling intrauterine device, hormonal implant/patch, injections, approved cervical ring) from Screening through LFU and for 90 days following the last dose.

Exclusion Criteria:

1. Presence of any known or suspected disease or condition that, in the opinion of the Investigator, 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, see Inclusion Criterion 4a])
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 IP (e.g., carbapenem-resistant pathogen), including infection caused by fungi (e.g., candiduria) or mycobacteria (e.g., urogenital tuberculosis)

2. Gross hematuria requiring intervention other than administration of IP or removal/placement of urinary tract instrumentation
3. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required relieving an obstruction or placing urinary tract instrumentation)
4. Creatinine clearance (CrCl) of ≤30 mL/min, as estimated by the Cockcroft-Gault formula:

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

5. Anticipated concomitant use of non-study antibacterial drug therapy between randomization and the LFU Visit that would potentially effect outcome evaluations of cUTI/ AP, including but not limited to antibacterials with potential activity versus uropathogens, antibacterial drug prophylaxis, and antibacterial bladder irrigation
6. Anticipated concomitant use of gastric acid-reducing medications between randomization and EOT, including proton pump inhibitors, histamine-2 receptor antagonists and antacids
7. Receipt of more than a single dose of a short-acting potentially effective antibiotic started within 72 h prior to randomization (see Appendix 2 for allowed single dose, short-acting antibiotics)

   Exception: Subjects who received more than a single dose of short-acting potentially effective antibiotic within 72 h prior to randomization may be eligible for enrollment if they meet all of the following criteria: (a) In the opinion of the Investigator they have failed the prior antibiotic therapy (e.g., have worsening signs and symptoms of cUTI/AP); (b) have a documented uropathogen (growth in urine

culture ≥10^5 Colony forming unit (CFU)/mL) that is resistant to the prior antibiotic therapy; (c) have a documented uropathogen that is carbapenem-susceptible; and (d) receives approval from the Medical Monitor to enroll the subject

8. Severe hepatic impairment at Screening, as evidenced by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x upper limit of normal (ULN) or total bilirubin >3x ULN, or clinical signs of cirrhosis or end-stage hepatic disease (e.g., ascites, hepatic encephalopathy)
9. Any signs of severe sepsis, including shock or profound hypotension defined as systolic blood pressure <90 mmHg or a decrease of >40 mmHg from baseline that is not responsive to fluid challenge
10. Pregnant or breastfeeding women
11. History of epilepsy or known seizure disorder (excluding a history of childhood febrile seizures)
12. Receipt of any 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 and acquired immunodeficiency syndrome (AIDS)-defining illness, or known history of HIV infection and known CD4 count <200/mm^3 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. A mean QT interval corrected using Fridericia's formula (QTcF) >480 msec based on triplicate electrocardiograms (ECGs) at Screening
16. History of significant hypersensitivity or allergic reaction to β-lactam antibiotics (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 ertapenem
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

Duration of Subject Involvement in the Study:

The duration of study participation for each subject is approximately 30 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 14: Subjects receive study drug (TBPM-PI-HBr or ertapenem) and dummy tablets or dummy infusions during this treatment period. The first dose of the study drug may occur on the same calendar day as the Screening Visit. The duration of study drug therapy will be 7-10 calendar days; however, if the subject has a positive Screening or Day 1 blood culture for uropathogen growth, the duration of study drug therapy may be extended to up to a maximum of 14 calendar days at the discretion of the Investigator.
- **End-of-Treatment (EOT) Visit** will be completed on the last day of study drug administration (Day 7-10, or up to Day 14 for bacteremic subjects), or the following day (e.g., allowing a 1 day window to complete EOT procedures with the exception of EOT ECGs which must be performed 1 hour (±15 min) after the last dose, rather than the following day). Subjects requiring more than 10 days of treatment (or more than 14 days of treatment for bacteremic subjects) will be discontinued from IP, assessed at EOT as clinical failure, and treated with an appropriate open-label antibiotic at the discretion of the Investigator. The subject will remain in the study for the remaining visits.
- **Test-of-Cure (TOC) Visit,** Day 19 (± 2 days) for all subjects.
- **Late Follow-Up (LFU) Visit,** Day 25 (± 2 days) for all subjects.

Statistical Considerations:

Analysis Populations:

- **Intent-to-Treat (ITT) Population**: All subjects who were randomized, regardless of whether they received any study drug. Subjects will be summarized by the treatment to which they were randomized.
- **Safety Analysis Population**: Randomized subjects who received any amount of study drug. Subjects will be summarized by the treatment which they received.
- **Microbiological Intent-to-Treat (micro-ITT) Population**: All randomized subjects with a confirmed diagnosis of cUTI or AP (Inclusion Criterion 4) and a positive Screening urine culture defined as growth of one or two uropathogens at $\geq 10^5$ CFU/mL. Subjects with Screening urine culture growth of more than 2 species of microorganisms will be excluded from the micro-ITT population, regardless of colony count. Any subject with cUTI or AP caused by a pathogen that is typically not expected to respond to either carbapenem study drug (e.g., *Acinetobacter* spp., *Stenotrophomonas* spp., *Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus* [MRSA]) will also be excluded from this population.
- **Clinically Evaluable (CE) Population**: Subjects who meet the definition for the ITT population, have no important protocol deviations that would affect the assessment of efficacy (to be defined in the Statistical Analysis Plan [SAP]), and

had an outcome assessed as clinical cure or clinical failure at EOT, TOC, and/or LFU.

- **Microbiologically Evaluable (ME) Population**: Subjects who meet the definitions of both the micro-ITT population and CE population.
- **PK Population**: All subjects treated with at least one dose of TBPM-PI-HBr with at least one analyzable plasma or urine PK sample.
- **Statistical Analysis**: The primary analysis will be the comparison of the overall response (clinical cure plus microbiological eradication) at the TOC Visit in the micro-ITT population. The 95% confidence interval (CI) will be calculated using the method of Mietennen and Nurminen. If the lower limit of the 95% CI for the difference in overall response is greater than or equal to -12.5%, non-inferiority will be declared. Other secondary analyses related to clinical response and microbiological response will present the 95% CI using the same method as for the primary endpoint.

In the setting of the ongoing COVID-19 pandemic, the statistical analyses and assessment of non-inferiority for the primary endpoint were revised in consultation with the US FDA, in order to preserve data integrity and to ensure the safety of patients and study team by limiting further enrollment into the study. The justification for this NI margin is provided in the June 2018 (Revision 1) FDA Guidance "Complicated Urinary Tract Infections: Developing Drugs for Treatment". This guidance demonstrates that the benefit of active antibacterial therapy over no treatment (M1) is estimated to be 30%. Therefore, an NI margin of -12.5% is deemed appropriate given the proposed margin is well below the M1 of 30% and retains greater than 50% of the clinical benefit (M1), whilst comparing TBPM-PI-HBr to an IV carbapenem comparator.

Presentation of safety data will be produced for the Safety Analysis population.

Assuming a response rate of 70% for both treatment groups, a pre-specified NI margin of 10%, a 1:1 randomization ratio, and a one-sided significance level of 0.025, a trial including 884 evaluable subjects would have approximately 90% power to show NI within a 10% margin. This trial aims to recruit 884 subjects for inclusion in the micro-ITT population. Assuming 75% of randomized subjects are included in the micro-ITT population, approximately 1,180 subjects will be recruited to ensure 884 subjects in the micro-ITT population. This size study would also have 90% power for an analysis of the ME population, assuming a 75% response rate and 67% of randomized subjects are included in the ME population. A blinded assessment of overall evaluability rates (the proportion of randomized subjects in the micro-ITT and ME populations) and response rates (pooled across treatment groups) will be performed during the study, and if assumptions are very different to those expected, the sample size may be increased according to pre-specified criteria.

Changes Due to the COVID-19 Pandemic:

At the time of the interim analysis (March 2020) the Data Review Committee (DRC) performed the planned blinded sample size reassessment after response data at TOC was available for 70% of patients. Based on the preliminary review of blinded data, the DRC recommended continuing recruitment up to the protocol-allowed maximum of 1,450

patients in order to ensure inclusion of 884 eligible patients in the primary analysis population.
Based on the DRC recommendation, enrollment in the study continued, however the rate of enrollment dramatically decreased in the setting of the global COVID-19 pandemic and related impact at multiple sites in countries where the study is being conducted. The Sponsor performed a continuous risk assessment in order to determine which sites could continue enrollment with minimal impact to patient/staff safety and post-treatment data collection. This ongoing risk assessment identified potential for significant impact to study conduct and data integrity based on difficulties in conducting post-treatment follow-up visits necessary for assessment of the primary endpoint, along with data monitoring of case records. Ultimately these challenges suggested that a progressively increasing proportion of indeterminate outcomes for the primary endpoint is likely with continued enrollment, which could bias the study towards non-inferiority. Therefore, the Sponsor, considered it in the best interest of the study, and study participants, to conclude enrollment and revise the planned analyses based on the available dataset.
Thus, the original NI margin of -10% was modified to -12.5% in consultation with FDA. Based on this modification, it is expected that at least 670 patients will be included in the micro-ITT population, which ensures that the study will have >90% power to show non-inferiority when using a -12.5% NI margin assuming a true response rate of at least 60% across both treatment groups.

Endpoints and Assessments:
Primary Endpoints:

1. Overall response (combined clinical cure plus microbiological eradication) at TOC in the micro-ITT population
    - 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
    - Microbiological eradication: Reduction of baseline urine pathogen(s) to $<10^3$ CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at baseline
2. Assessment of treatment emergent adverse events (TEAEs), clinical laboratory (hematology, clinical chemistry, and urinalysis) changes, ECGs, and vital sign changes in the Safety Analysis population

Secondary Endpoints:

1. Overall response (combined clinical cure plus microbiological eradication as defined above) at the TOC Visit in the ME population
2. Clinical cure at EOT, TOC, and LFU Visits in the micro-ITT, CE, and ME populations
3. By-subject and by-pathogen microbiological eradication at EOT, TOC, and LFU in the micro-ITT and ME populations
4. Overall response in subgroups, including:
    - Stratified infection category
    - Stratified age category

- Country/Region

5. Time (days) to resolution or improvement of signs and symptoms of cUTI and AP present at baseline in the micro-ITT populations
6. Time (days) to defervescence in micro-ITT subjects with a documented fever at Screening or Day 1
7. Rate of clinical relapse at the LFU Visit in the micro-ITT population
8. Rates of superinfection and new infection in the micro-ITT population
9. Determine PK parameters (e.g., Vd, C_{max}, AUC, T>MIC) in TBPM-PI-HBr recipients in the PK population

Exploratory Endpoints:

1. Enteric colonization with antibiotic-resistant *Enterobacteriaceae* at the TOC Visit in the micro-ITT population
2. By-subject and by-pathogen microbiological eradication and by-subject and by-pathogen clinical improvement at Day 5 in the micro-ITT, CE, and ME populations
3. Clinical, microbiological, and overall responses at TOC among subjects with cUTI/AP caused by ESBL-producing *Enterobacteriaceae*

Safety:

Assessments of safety will include the following:

- Clinical observations
- Vital sign measurement
- Laboratory tests
- Physical examination
- ECG
- Reported adverse events

Some key safety endpoints will include:

- Frequency of adverse events by severity, seriousness, system organ class, preferred term, and treatment group
- Change from baseline in selected laboratory assays, including WBC count, hemoglobin (Hb), liver function tests (AST, ALT, ALP), BUN, serum creatinine (Cr), and estimated Cr clearance (based on Cockcroft-Gault formula) by treatment group and L-carnitine
- Grade shift in selected laboratory assays from baseline
- Change from baseline in vital signs

Pharmacokinetics:

The PK population includes all subjects treated with at least one dose of TBPM-PI-HBr with at least one analyzable plasma or urine PK sample. The PK population includes two sets of TBPM-PI-HBr-treated subjects, the Sentinel PK Analysis Group and the Sparse PK Analysis Group:

Sentinel PK Analysis Group (first approximately 35 TBPM-PI-HBr-treated subjects among the first approximately 70 subjects enrolled):

- Plasma PK Assessments: Blood samples will be collected following an oral dose (first, second, or third) on Day 2 at the following time intervals after oral administration of study drug: 0.25 h (±5 min); 0.5 h (±5 min); 1 h (±15 min); 2 h (±15 min); 8 h (±15 min but prior to the next scheduled dose). These samples will be used to estimate PK parameters, such as AUC, C_{max}, T_{max}, CL, $t_{1/2}$, C_{min}, and V_{SS}.
- Urine PK Assessments: Twenty-four (24) h urine collection will be collected roughly in three (3) 8-h aliquots starting on Day 1. TBPM concentrations will be measured and total 8h, 16h, and 24h urine elimination will be estimated.

Sparse PK Analysis Group (All subjects enrolled after the first approximately 70 subjects):

- Plasma PK Assessments: Blood samples, using sparse sampling (3 samples/subject), will be collected following an oral dose (first, second, or third) on Day 2 of treatment at the following time intervals after oral administration of study drug: 1 h (± 15 min); 4h (±1h); and 8 h (±30 min but prior to the next scheduled dose).

- Urine PK Assessments will not be performed for this set of subjects.

Masked individual and composite PK data from the first approximately 35 TBPM-PI-HBr-treated subjects enrolled (among the first approximately 70 total subjects enrolled) will be reviewed by a blinded, independent PK Data Review Committee to verify the TBPM-PI-HBr dose. This review will be blinded and will only be a review of PK data; this is not a formal review of safety or efficacy. PK samples obtained from the TBPM-PI-HBr group will be analyzed using a validated assay by a central bioanalytical laboratory. Study enrollment will continue uninterrupted during this blinded, interim PK data assessment, and the remaining subjects will undergo sparse PK sampling. If TBPM-PI-HBr dose alteration needs to be considered, enrollment may be paused for sample size adjustment and protocol amendment. If a change in dose is required, the planned total enrollment may be adjusted as needed to ensure sufficient data are available from 884 evaluable subjects receiving the amended dose (Section 9.13).

Data Safety Monitoring Board (DSMB):

A DSMB will be involved in the management of this study to review safety. The DSMB will review safety data upon enrollment of 25% and 50% of subjects. Full details regarding the DSMB (e.g., committee composition, the criteria for scheduling an ad hoc meeting, what will be presented/decided) will be specified in the DSMB charter. The DSMB charter will be approved and finalized by the DSMB members prior to the first meeting.

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ABBREVIATIONS

AE	**Adverse Event**
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AP	Acute pyelonephritis
API	Active Pharmaceutical Ingredient
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the concentration-time curve estimated from time zero to infinity as the sum of the 2 areas: AUC_{0-t} and AUC_{extrap}, where AUC_{extrap} is calculated as C_t / λ_z
AUC_{0-t}	Area under the concentration versus time curve from time zero to the sampling time at the last quantifiable concentration (C_t) at the time of the last quantifiable concentration (t_{last}) calculated by the linear trapezoidal rule
AUC_{extrap}	Area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of total AUC
BPH	Benign prostatic hyperplasia
BUN	Blood Urea Nitrogen
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CDC	Centers for Disease Control and Prevention
CE	Clinically Evaluable
CFU	Colony forming unit
CI	Confidence interval
CL	The systemic clearance calculated as: $Dose/AUC_{0-oo}$
Cr	Creatinine
CrCl	Creatinine clearance
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
cUTI	Complicated urinary tract infection

AE	Adverse Event
dL	Deciliter
DRC DSMB	Data Review Committee Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EC	Ethics Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
EOT	End-of-Treatment
ESBL	Extended Spectrum Beta-Lactamase
EU	European Union
FDA	Food and Drug Administration
FOCP	Females of childbearing potential
FPI	First Patient In
g	gram
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
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
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product (tebipenem pivoxil hydrobromide 300 mg film-coated tablets and comparator)
IR	Immediate release
IRB	Institutional Review Board

AE	**Adverse Event**
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web Response System
LC/MS/MS	Liquid chromatography tandem mass spectrometry
LE	Leukocyte esterase
LFU	Late Follow-Up
LPO	Last Patient Out
MDR	Multidrug-resistant
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MIC	Minimum inhibitory concentration
micro-ITT	Microbiological Intent-to-Treat
min	minutes
mL	milliliter
mm^3	Cubic millimeter
NCS	Not clinically significant
NI	Non-inferiority
OTC	Over-the-Counter
PI	Principal Investigator
PK	Pharmacokinetic(s)
PMN	Polymorphonuclear neutrophils
PO	Orally
QTcF	Fridericia's formula
qXh	Every X hours
QD	Once daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction

AE	Adverse Event
λz	Terminal disposition rate constant/terminal rate constant
T>MIC	The time above the minimum inhibitory concentration
$t_{½}$	The apparent terminal half-life, calculated from Ln 2 / λz
T_{max}	Time at which Cmax was apparent
TBPM	Tebipenem
TBPM-PI	Tebipenem pivoxil
TBPM-PI-HBr	Tebipenem pivoxil hydrobromide
TEAE	Treatment Emergent Adverse Event
TOC	Test-of-Cure
ULN	Upper Limit of Normal
US	United States
UTI	Urinary tract infection
uUTI	Uncomplicated urinary tract infection
Vd	The apparent volume of distribution, calculated as the amount of drug in the body divided by the concentration of drug in the blood/plasma
V_{SS}	The apparent volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization

1. BACKGROUND INFORMATION

1.1. Condition Background and Current Treatment

Tebipenem pivoxil hydrobromide (TBPM-PI-HBr), also known as SPR994, is under investigation by Spero Therapeutics, Inc. (Spero) to treat serious life-threatening infections with unmet need. The current indication under investigation is for the treatment of complicated urinary tract infection (cUTI) including AP.

1.2. Product Background

Tebipenem (TBPM) is a broad-spectrum antibiotic from the carbapenem subgroup of β-lactam antibiotics. Tebipenem pivoxil (TBPM-PI), a pivaloyloxymethyl prodrug of TBPM, is administered orally due to the better absorption and improved bioavailability of this prodrug form. TBPM-PI is currently marketed only in Japan (Meiji Seika Pharma Co., Ltd, "Meiji") as a pediatric granule formulation (Orapenem® Fine Granules 10%) for pediatric use in the treatment of otitis media, sinusitis, and pneumonia.

TBPM-PI-HBr, Spero's proprietary hydrobromide salt form of TBPM-PI, is being developed to improve drug substance and drug product properties including stability.

Based on the outcome of the SPR994-101 study, an immediate release formulation (600 mg, q8h [±0.5 h]) has been selected for the ADAPT-PO (SPR994-301) study.

1.2.1. Preclinical Information

Please refer to the current Investigator's Brochure (IB) for detailed information regarding preclinical safety data.

The pharmacokinetic (PK) profile of TBPM-PI-HBr (IR formulation) has been demonstrated to be similar to that of TBPM-PI both with *in vitro* dissolution and *in vivo* dog and monkey PK studies. In addition, TBPM-PI-HBr and TBPM-PI both metabolize to TBPM and the Sponsor views the toxicity profile of TBPM-PI as representative and supportive of TBPM-PI-HBr. Further, the toxicology studies in rats and cynomolgus monkeys indicate that the target organ of toxicity is the GI tract as demonstrated by the diarrhea, vomiting, and gastric irritancy of TBPM-PI, which is consistent with the clinical safety profile observed in studies conducted by Meiji.

In single dose toxicity studies, the acute toxicity of TBPM-PI in rats and monkeys was assessed. In repeated-dose toxicity studies, rats and monkeys were administered TBPM-PI for 28 days, observed for clinical signs, body weight, food consumption, and organ weights, and underwent ophthalmology, urinalysis, hematology, clinical chemistry, necropsy with macroscopic assessment of tissues, and histopathology. Genotoxicity studies of TBPM-PI and TBPM included bacterial reverse mutation, chromosome aberration, and gene mutation studies. Additionally, TBPM-PI *in vivo* genetic toxicology studies including bone marrow micronucleus, liver unscheduled DNA synthesis, and gastrointestinal single cell gel studies were conducted. Reproductive and developmental toxicity studies conducted in mice, rats, and monkeys included embryo-fetal development. No toxicity studies of metabolites were

conducted because there are no human-specific metabolites of TBPM-PI identified, as such; all metabolites that may be formed in humans have been fully assessed in the current nonclinical studies.

1.2.2. Clinical Information

Please refer to the current IB for detailed information regarding clinical safety data.

TBPM-PI is a carbapenem antibiotic and has demonstrated a similar safety profile to other carbapenems. In studies conducted by Meiji, the most common adverse events (AEs) were gastrointestinal (GI) AEs, in children and adults. Diarrhea was also documented as a common AE, and sometimes severe in children younger than 3 years, but was less frequent in adults with no severe or serious GI AEs reported. Skin disorders such as rash occurred infrequently in children and adults with few discontinuations, and none were serious. Transient increases in hepatic enzymes occurred in less than 10% of adults and resolved or were resolving upon discontinuation; no hepatic SAEs or severe events were reported. Though decreases in serum carnitine were observed, no associated AEs were reported; these observations in humans are consistent with the 28-day toxicity study where decreases in serum total carnitine levels were observed at all dose levels without any relevant toxicological change SAEs in both children and adults appear to have been incidental to administration. Additional safety considerations with the use of TBPM-PI include avoidance of use with valproic acid, caution in individuals with a history of carbapenem-, penicillin-, and cephalosporin-antibiotics sensitivity and adjustment of dose in individuals with advanced renal impairment.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Rationale for the Study

There is a great need for alternative oral therapies for the treatment of cUTI and AP caused by multidrug-resistant (MDR) Gram-negative pathogens, including ESBL-producing *Enterobacteriaceae* and pathogens resistant to commonly used agents such as fluoroquinolones, aminoglycosides, and trimethoprim/sulfamethoxazole. The Centers for Disease Control and Prevention (CDC) estimates that an estimated 140,000 healthcare-associated *Enterobacteriaceae* infections occur annually in the US with 26,000 drug-resistant infections and 1,700 deaths caused by ESBL-producing *Enterobacteriaceae*. Of these healthcare- associated infections, the CDC estimates that 17,000 are attributable to ESBL-producing *Klebsiella* spp. and 9,000 are attributable to ESBL-producing *Escherichia coli* (*E. coli*) (CDC 2013). Urinary tract infections in the US due to fluoroquinolone-resistant pathogens are now >10% and as high as 50% is some hospital centers (Talan 2016).

E. coli is the most common cause of UTI and AP, whether complicated or uncomplicated. Until recently, fluoroquinolones were the preferred agents for treating cUTI and AP; however, fluoroquinolone resistance is rapidly spreading. This is in part due to the global spread of a uropathogenic *E. coli* clone, ST131, which harbors a number of ESBLs, particularly CTX-M-15, which has become one of the predominant CTX-M type β-lactamases in the world. ESBLs render these uropathogenic strains resistant to all β-lactams except carbapenems. In addition, *E. coli* ST131 strains also carry resistance to trimethoprim/sulfamethoxazole and aminoglycosides. Unfortunately, a subclone H30 ST131 that also brings fluoroquinolone resistance has emerged and become prevalent in the US. This subclone appears to have several advantages that will continue to drive its clinical dominance, including a broad host range and adaptive mutations that confer greater fitness in the pathologic niche. The rise of fluoroquinolone resistance in the US has been dramatic in the last decade (Johnson 2013), and cUTI caused by this MDR strain currently requires IV therapy with a carbapenem.

TBPM-PI-HBr administered orally may provide a favorable alternative therapy for subjects experiencing cUTI caused by ESBL-producing MDR pathogens. Considering the rising prevalence of fluoroquinolone-resistant, ESBL-producing *E. coli*, this is an important unmet need. Alternative oral options such as TBPM-PI-HBr may be expected to decrease the need for hospitalization and the use of venous catheterization, thus reducing costs and associated complications.

Tebipenem exhibits antibacterial activity against most Gram-negative pathogens frequently implicated in UTI, including *E. coli* and *Klebsiella pneumoniae* (Mendes et al., 2018, Muratani et al., 2009). *E. coli* is the most common pathogen causing both community-associated and healthcare-associated UTI (Doi et al., 2013). In recent years, many of these organisms have been shown to harbor MDR mechanisms that include extended spectrum β-lactamases (ESBLs) and/or AmpC β-lactamases that limit the effectiveness of many of the currently available oral step down agents such as the fluoroquinolones and trimethoprim-sulfamethoxazole. In common with other carbapenems such as ertapenem, tebipenem maintains antibacterial activity against both the ESBL and/or AmpC β-lactamase-producing

organisms collected from subjects with UTI in the US and Europe during 2016 (Mendes et al, 2018). Like other carbapenems, tebipenem does not have antibacterial activity against carbapenemase-producing *Enterobacteriaceae* (KPC and metallo-β-lactamase producing organisms). The potent *in vitro* activity of tebipenem also translates to *in vivo* efficacy in a murine ascending *E. coli* urine tract infection model, where significant reduction in bacterial burden was observed in the kidney, bladder and urine (Heang et al, 2018). Tebipenem displays efficacy in multiple animal models of infection caused by a broad range of pathogens (Yao 2016, Fujimoto 2013, and Meiji J-NDA). Collectively these data provide support for the clinical development of tebipenem and an oral option for treating cUTI/AP.

Ertapenem was chosen as the comparator for this study because it is approved for the treatment of cUTI/AP in many countries, and is considered an empiric standard-of-care treatment option. Ertapenem has bactericidal activity against primary pathogens that cause cUTI/AP, including extended spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*. Ertapenem is associated with high urinary concentrations, has a similar *in vitro* spectrum of activity, and is in the same antibiotic class (carbapenem) as TBPM-PI-HBr.

2.1.1. Primary Objectives

The primary objectives are:

- To assess the overall response (combined clinical cure plus microbiological eradication) of oral TBPM-PI-HBr compared to IV ertapenem in subjects ≥18 years of age with cUTI/AP
- To assess the safety of oral TBPM-PI-HBr compared to IV ertapenem in subjects ≥18 years of age with cUTI/ AP

2.1.2. Secondary Objectives

The secondary objectives are:

- To compare clinical cure rates between treatment groups
- To compare microbiological eradication rates between treatment groups
- To assess the population PK of TBPM-PI-HBr in subjects with cUTI/AP; the dosage of TBPM-PI-HBr will be confirmed based off a blinded analysis of PK data from the first approximately 35 enrolled TBPM-PI-HBr subjects

2.1.3. Exploratory Objectives

The exploratory objectives are:

- To determine whether treatment with TBPM-PI-HBr or ertapenem is associated with enteric colonization with antibiotic-resistant *Enterobacteriaceae*
- To compare microbiological eradication rates and clinical improvement at Day 5 between treatment groups

- To assess clinical, microbiological, and overall responses in subjects with cUTI/AP caused by ESBL-producing *Enterobacteriaceae*

3. STUDY DESIGN

3.1. Study Design

This is a Phase 3, randomized, double-blind, double-dummy, multicenter, multinational, prospective study to assess the efficacy, safety and PK of TBPM-PI-HBr administered orally compared with ertapenem administered IV for cUTI/AP.

This study will enroll approximately 1,200 subjects, up to a maximum of 1,450 subjects (contingent upon a sufficient number of evaluable subjects; Section 9.13). For this study, enrollment occurs at the time of randomization, and it is expected that more subjects will be screened than enrolled into the study. All subjects with a clinical diagnosis of cUTI/AP sufficient to start empiric antibiotics, and who are able to tolerate oral medication will be randomly assigned to one of the following groups:

- TBPM-PI-HBr: 600 mg (2 tablets) PO q8h (±0.5 h) plus dummy IV infusion q24h (±0.5 h) (n=600); subjects with moderate renal insufficiency (CrCl >30 to ≤50 mL/min) require TBPM-PI-HBr dosage adjustment to 300 mg (1 tablet) q8h ± 0.5
- Ertapenem: 1 gram IV q24h (±0.5 h) plus dummy oral tablets q8h (±0.5 h) (n=600)

A dummy infusion of normal saline and dummy placebo tablets will be used to maintain the blind.

Day 1 is the first day of study drug administration. The duration of study drug therapy will be 7-10 calendar days; however, if the subject has a positive Screening or Day 1 blood culture for uropathogen growth, the duration of study drug therapy may be extended to up to a maximum of 14 calendar days at the discretion of the Investigator. Subjects who are prematurely discontinued from study drug dosing should undergo all End-of-Treatment (EOT) Visit procedures and should be followed through the Late Follow-Up (LFU) Visit for safety assessments, regardless of the reason for early study drug discontinuation.

Randomization will be stratified by baseline infection type (AP and cUTI) and age (≥18 to <65 years, ≥65 years). Subjects who meet the disease definition of cUTI (e.g., underlying functional or anatomical urinary tract abnormality) and have additional clinical evidence of AP (e.g., flank pain or costovertebral angle tenderness) should be randomized as cUTI. At least 30% of subjects will be randomized with a diagnosis of AP at study entry.

Receipt of any potentially effective systemic antibiotic with activity against Gram-negative uropathogens within the 72 h window prior to randomization is an exclusion criterion. However, subjects who received a single dose of a short-acting systemic antibiotic up to 72 h prior to randomization (see Appendix 2 for list of allowed short-acting antibiotics) may be randomized up to a maximum of 25% of the study enrollment. In this study, a short-acting antibiotic is defined as having a dosage frequency of more than once daily (e.g., q12 h or more frequently).

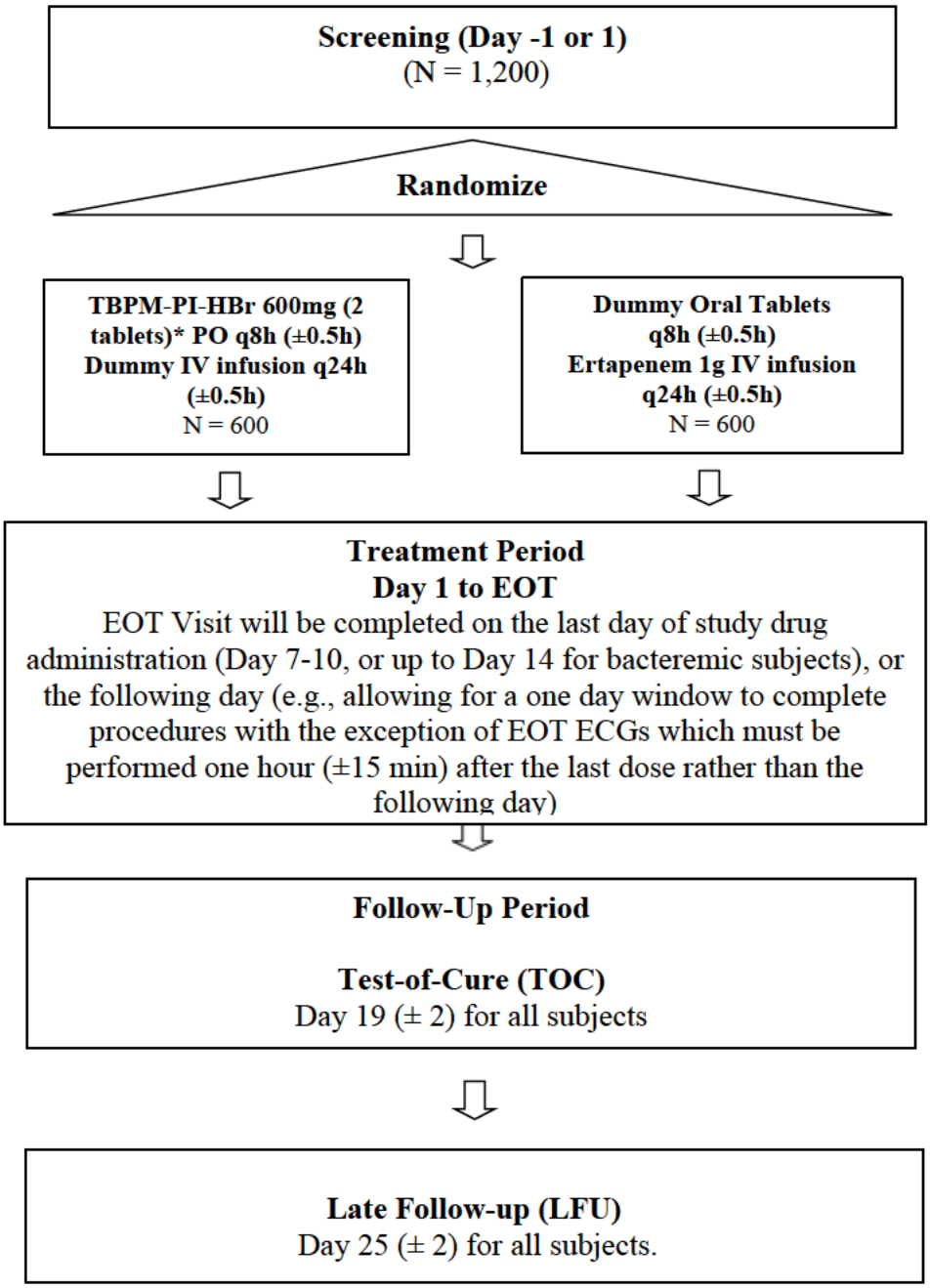
All organisms isolated from blood or urine cultures will be identified to the genus and species level. Uropathogens isolated from blood or urine cultures will be cultured and quantified at the local/regional laboratory, and antimicrobial susceptibility testing may be performed per

local standards of care (including carbapenem susceptibilities); however, specific susceptibility testing for TBPM-PI-HBr will not be available to the local/regional laboratories and will only be performed at the central laboratory. All baseline or post-baseline urine culture isolates that grow $\geq 10^3$ Colony forming unit (CFU)/milliliter (mL), and all blood culture isolates, will be sent to the central laboratory for identification and susceptibility testing, and stored for possible further characterization of the organisms. Additional details are provided in a laboratory manual.

Although local susceptibility testing is not a requirement, when local susceptibility testing indicates non-susceptibility to study drug (e.g., intermediate susceptibility or resistance to a carbapenem antibiotic) but the subject is stable or clinically improving, the subject should remain on blinded study drug at the Investigator's discretion. Similarly, if baseline blood cultures become positive after randomization but the subject is stable or clinically improving, the subject should remain on blinded study drug at the Investigator's discretion. In such cases, prior to premature discontinuation from study drug, the Investigator should discuss the cases with the Medical Monitor. Subjects will be hospitalized for the duration of their treatment. Exceptions may be made for US sites that have qualified, Sponsor-approved outpatient infusion centers for receipt of daily-blinded IV study drug (ertapenem or placebo), provided study staff is able to manage all required study activities in the subject setting.

After the first approximately 70 subjects have been enrolled, masked individual and composite PK data will be reviewed by a blinded, independent PK Data Review Committee to verify the TBPM-PI-HBr dose. This review will occur after approximately 70 subjects in order for the PK assessment to include approximately 35 subjects receiving TBPM-PI-HBr. PK samples obtained from the TBPM-PI-HBr group will be analyzed using a validated assay by a central bioanalytical laboratory. Study enrollment will continue uninterrupted during this blinded, interim PK data assessment, and the remaining subjects (approximately 1,130 subjects) will undergo sparse PK sampling. If TBPM-PI-HBr dose alteration needs to be adjusted, enrollment may be paused for sample size adjustment and protocol amendment. If a change in dose is required, the planned total enrolment may be adjusted as needed to ensure sufficient data are available from 884 evaluable subjects receiving the amended dose (Section 9.13).

Figure 1: Study Design Flow Chart



*TBPM-PI-HBr requires dosage adjustment to 300 mg (1 tablet) PO q8h (±0.5h) in subjects with moderate renal insufficiency (CrCl >30 to ≤50 mL/min).

3.2. Number and Type of Subjects

Approximately 1,200 subjects aged ≥18 years with cUTI/AP will be enrolled in the study, up to a maximum of 1,450 (contingent on a sufficient number of evaluable subjects; Section 9.13). For this study, enrollment occurs at the time of randomization. It is expected that more subjects will be screened than enrolled into the study.

3.2.1. Investigational Product

- TBPM-PI-HBr 300 mg film-coated tablet:
  - For subjects with normal renal function or mild renal insufficiency (CrCl >50 mL/min): 600 mg (2 tablets) PO q8h (±0.5 h) plus dummy IV infusion q24h (±0.5 h)
  - For subjects with moderate renal insufficiency (CrCl >30 to ≤50 mL/min): 300 mg (1 tablet) PO q8h (±0.5 h) plus dummy IV infusion q24h (±0.5 h)
- Ertapenem: 1gram IV q24h (±0.5 h) for all subjects (CrCl >30 mL/min)
  - Plus 2 dummy oral tablets q8h (±0.5 h) for subjects with normal renal function or mild renal insufficiency (CrCl >50 mL/min)
  - Plus 1 dummy oral tablet q8h (±0.5 h) for subjects with moderate renal insufficiency (CrCl >30 to ≤50 mL/min)
- A dummy infusion of normal saline (0.9%) and dummy placebo tablets will be used to maintain the blind

3.3. Sites and Regions

Approximately 95 sites in Central and Eastern Europe, South Africa, and the United States are planned for this study.

4. STUDY POPULATION

4.1. Inclusion Criteria

1. Male and female subjects at least 18 years of age
2. Able to provide informed consent
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, in order to tolerate oral study drug.
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; fever must be observed and documented by a health care provider (oral, tympanic, rectal or core temperature >38.0°C [>100.4°F])
      ii. Dysuria, urgency to void, or increased urinary frequency
      iii. Nausea or vomiting, as reported by the subject
      iv. Lower abdominal, suprapubic, or pelvic pain

      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 hours 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 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)
      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:

v. Chills, rigors, or fever; fever must be observed and documented by a health care provider (oral, tympanic, rectal or core temperature >38.0°C [>100.4°F])
vi. Peripheral white blood cell count (WBC) $\geq$10,000/mm^3 or bandemia ($\geq$15% immature polymorphonuclear neutrophils [PMNs], regardless of WBC count)
vii. Nausea or vomiting, as reported by the subject
viii. Dysuria, urgency to void, or increased urinary frequency

Note: Subjects who meet the definition for cUTI (Inclusion Criterion 4a) and also 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 cubic millimeter (mm^3) in unspun urine
   c. Positive LE on urinalysis

   Note: Subjects may be randomized and administered IP prior to knowledge of urine culture results.
6. Expectation, in the judgment of the Investigator, that the subject will survive with effective antibiotic 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. Subjects must agree to use a highly-effective method of birth control; male subjects must agree to use an effective barrier method of contraception from Screening through LFU and for 90 days following the last dose if sexually active with a female of childbearing potential (FOCP); female subjects must not be pregnant or nursing, and must commit to either sexual abstinence or use at least two medically accepted, effective methods of birth control (e.g., condom, spermicidal gel, oral contraceptive, indwelling intrauterine device, hormonal implant/patch, injections, approved cervical ring) from Screening through LFU and for 90 days following the last dose.

4.2. Exclusion Criteria

1. Presence of any known or suspected disease or condition that, in the opinion of the Investigator, may confound the assessment of efficacy, including but not limited to the following:
   a. Perinephric or renal corticomedullary abscess
   b. uUTI (acute cystitis that does not meet the cUTI disease definition, see Inclusion Criterion 4a)
   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 IP (e.g., carbapenem-resistant pathogen), including infection caused by fungi (e.g., candiduria) or mycobacteria (e.g., urogenital tuberculosis)

2. Gross hematuria requiring intervention other than administration of IP or removal/placement of urinary tract instrumentation
3. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required relieving an obstruction or placing urinary tract instrumentation)
4. Creatinine clearance (CrCl) of ≤30 mL/min, as estimated by the Cockcroft-Gault formula:

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

5. Anticipated concomitant use of non-study antibacterial drug therapy between randomization and the LFU Visit that would potentially effect outcome evaluations of cUTI/ AP, including but not limited to antibacterials with potential activity versus uropathogens, antibacterial drug prophylaxis, and antibacterial bladder irrigation
6. Anticipated concomitant use of gastric acid-reducing medications between randomization and EOT, including proton pump inhibitors, histamine-2 receptor antagonists, and antacids
7. Receipt of more than a single dose of a short-acting potentially effective antibiotic started within 72 h prior to randomization (see Appendix 2 for allowed single dose, short-acting antibiotics)

   Exception: Subjects who received more than a single dose of short-acting potentially effective antibiotic within 72 h prior to randomization may be eligible for enrollment if they meet all of the following criteria:

   a. In the opinion of the Investigator they have failed the prior antibiotic therapy (e.g., have worsening signs and symptoms of cUTI/AP)
   b. Have a documented uropathogen (growth in urine culture $\geq 10^5$ CFU/mL or in blood) that is resistant to the prior antibiotic therapy
   c. Have a documented uropathogen that is carbapenem-susceptible
   d. Receives approval from the Medical Monitor to enroll the subject

8. Severe hepatic impairment at Screening, as evidenced by alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x upper limit of normal (ULN) or total bilirubin >3x ULN, or clinical signs of cirrhosis or end-stage hepatic disease (e.g., ascites, hepatic encephalopathy)
9. Any signs of severe sepsis, including shock or profound hypotension defined as systolic blood pressure <90 mmHg or a decrease of >40 mmHg from baseline that is not responsive to fluid challenge
10. Pregnant or breastfeeding women
11. History of epilepsy or known seizure disorder (excluding a history of childhood febrile seizures)
12. Receipt of any 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 and acquired immunodeficiency syndrome (AIDS)-defining illness, or known history of HIV infection and known CD4 count <200/mm^3 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. A mean QT interval corrected using Fridericia's formula (QTcF) >480 msec based on triplicate ECGs at Screening
16. History of significant hypersensitivity or allergic reaction to β-lactam antibiotics (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 ertapenem
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

4.3. Reproductive Potential

Female subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea and age ³51 years), or
- Surgically sterile and at least 6 weeks post-sterilization, or
- Subjects with a negative pregnancy test at the Screening Visit prior to randomization and who are using or agree to use acceptable methods of contraception.

Condoms should be used with the following acceptable contraceptives:

- Intrauterine devices
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring)

Other acceptable contraception methods are:

- Double barrier methods (e.g., condoms and diaphragms with spermicidal gel or foam)
- Sexual abstinence

Sexually active FOCP must agree to use an acceptable form of contraception. FOCP must be advised to use acceptable contraceptives throughout the study period and for 90 days following the last dose of IP. If hormonal contraceptives are used, they should be administered according to the package insert. FOCP who are not currently sexually active must agree to use acceptable contraception, as defined above, if they become sexually active during the period of the study, and for 90 days following the last dose of IP. Male subjects must agree to use an effective barrier method of contraception during the study and for 90 days following the last dose if sexually active with a FOCP.

4.4. Withdrawal from Study

Subjects 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 subject withdraws consent or requests withdrawal from the study for any reason
- The subject is lost to follow-up
- The subject fails to comply with protocol requirements or study-related procedures
- The Investigator determines that it is in the best interest of the subject 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 for any reason, including but not limited to study drug-related unexpected life-threatening SAEs detected during safety monitoring (e.g., Torsade des Pointes or other ventricular arrhythmias)

Subjects 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.

Subjects who withdraw from the study should be assessed as indeterminate at EOT, TOC, and/or LFU, as appropriate at the time of withdrawal.

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

4.5. Premature Discontinuation of Investigational Product

Premature discontinuation of investigational product by the Investigator is an important discussion, which should include the Medical Monitor, if feasible, before IP is discontinued.

Possible reasons for premature discontinuation from IP 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 subject's permanent discontinuation from IP 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, and no other disease or condition can be found to explain the liver test abnormalities; or known pregnancy or breastfeeding during the study drug administration period; decline in post-baseline renal function such that the estimated CrCl falls to ≤30 mL/min (Section 6.2.5).

Subjects prematurely discontinued from IP for safety reasons and for whom further antibacterial 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 antibacterial therapy is necessary), may be assessed as a clinical cure at the EOT and TOC Visits. Subjects prematurely discontinued from IP for safety reasons and who require further antibacterial therapy for the cUTI/AP should be assessed as a clinical and microbiological failure at EOT and TOC.

Possible reasons for discontinuation from IP *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 IP continuance acceptable, study drug administration of at least 48 h is encouraged before discontinuation from IP therapy for insufficient effect.

Refer to Section 9.10.1 on handling of data for patients who discontinue IP.

Subjects who are prematurely discontinued from IP administration should remain in the study and continue to undergo study assessments at every subsequent study visit (e.g., TOC, LFU), and *not* be withdrawn from study.

4.6. Subjects Lost to Follow-up Prior to Last Scheduled Visit

At least 3 documented attempts must be made to contact any subject 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 subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they

return any unused IP, if applicable, and return to the site for final safety evaluations. The return of unused IPs will be handled at individual sites.

5. PRIOR AND CONCOMITANT TREATMENT

For purposes of evaluating inclusion criteria, all prior treatment includes all treatment (including over-the-counter [OTC] treatments such as herbal treatments, vitamins, diet aids, and hormone supplements; and non-pharmacological treatment such as psychotherapy as appropriate) received within 30 days prior to the date of first dose of IP.

Subjects who had antibacterial drug therapy started within 72 h prior to enrollment may only be randomized if they meet the exception in Exclusion Criterion 7, as follows:

Subjects who received more than a single dose of short-acting potentially effective antibiotic started within 72 h prior to randomization may be eligible for enrollment if they meet all of the following criteria:

a. In the opinion of the Investigator they have failed the prior antibiotic therapy (e.g., have worsening signs and symptoms of cUTI/AP)
b. Have a documented uropathogen (growth in urine culture $\geq 10^5$ CFU/mL or in blood) that is resistant to the prior antibiotic therapy
c. Have a documented uropathogen that is carbapenem-susceptible
d. Receives approval from the Medical Monitor to enroll the subject

Any subject record of prior treatment must be documented on the appropriate Case Report Form (CRF) page.

5.1. Concomitant Treatment

Concomitant treatment taken between the dates of the first dose of IP and the last study visit, inclusive, are to be listed on the appropriate CRF page.

Concomitant administration of additional or adjunctive non-study-specific, potentially effective, systemic antibiotic therapy for reasons other than clinical failure of IP (in treating the index cUTI/ AP) is not allowed. Questions regarding the use of concomitant non-study-specific systemic antibiotic therapy should be directed to the Medical Monitor prior to administration.

6. INVESTIGATIONAL PRODUCT

6.1. Identity of Investigational Product

The IP is TBPM-PI-HBr, the hydrobromide salt of pivoxil prodrug of TBPM, which will be administered orally as one or two 300 mg film-coated, immediate release tablets, depending on renal function. The pivoxil prodrug enables high oral absorption and improved bioavailability of tebipenem (Kato 2010) while the hydrobromide salt form improves the drug substance and drug product properties, including stability. TBPM is active against Gram-negative and Gram-positive pathogens that cause serious and life-threatening infections, including ESBL producers as well as strains resistant to levofloxacin and trimethoprim/sulfamethoxazole.

The comparator is ertapenem, a commercially available carbapenem (β-lactam antibiotic) with a similar spectrum of microbiologic activity to that described for TBPM-PI-HBr. Ertapenem will be provided as a sterile, lyophilized powder packaged in vials. Each vial contains 1.046 g ertapenem sodium equivalent to 1 g of ertapenem for IV infusion following reconstitution and dilution. Please refer to the Summary of Product Characteristics (SmPC)/ Product Package Insert for detailed information regarding ertapenem.

TBPM-PI-HBr tablets will be supplied by a designated manufacturer/vendor of Spero Therapeutics, Inc., and commercially available ertapenem will be procured from a qualified manufacturer/vendor. Standard operating procedures will be followed for the receipt, handling, and accountability of the study formulations.

A Normal saline solution (0.9%) and water for injection for dummy/placebo and ertapenem infusions will be supplied. Placebo tablets (300 mg) are pressed from a single placebo blend consisting of the same inactive ingredients as active TBPM-PI-HBr and Mannitol 200SD Microcrystalline cellulose, which replaces the API.

Spero Therapeutics, Inc. or designee will provide study sites with a sufficient quantity of IP supplies.

6.2. Administration of Investigational Product(s)

6.2.1. Interactive Web Response System for Investigational Product Management

An Interactive Web Response System (IWRS) is used for IP management tasks. This may include, for example, randomization, IP supply management, inventory management and supply ordering, IP expiration tracking, and emergency unblinding.

6.2.2. Dosing in Subjects with CrCl >50 mL/min

Eligible subjects with a clinical diagnosis of cUTI/AP sufficient to start empiric antibiotics, have normal renal function or mild renal insufficiency (CrCl >50 mL/min), and who are able to tolerate oral medication will be randomly assigned at a 1:1 ratio to one of the following groups:

- **TBPM-PI-HBr**: 600 mg (2 tablets) PO q8h (±0.5 h) plus dummy placebo (0.9% normal saline) IV infusion administered in a total volume of 60 ml over 30 minutes q24h (±0.5 h)

  Note: Dose adjustment is required for subjects with estimated baseline CrCl ≤50 mL/min as outlined in Section 6.2.4. However, for subjects who have a baseline/screening 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), the Investigator may choose to administer TBPM-PI-HBr 600 mg, as a single initial dose while reassessing the need for a dosage adjustment based on a subsequent CrCl assessment (see Section 6.2.4 for details).

- **Ertapenem**: 1 gram administered by IV infusion in a total volume of 60 mL over 30 min q24h (±0.5 h) plus 2 dummy placebo tablets administered orally q8h (±0.5 h)

Dosing of oral study drug tablets may be administered irrespective to the timing of meals. The administration of TBPM-PI-HBr with or without food was previously evaluated in a study in healthy volunteers which demonstrated negligible differences in the absorption or systemic exposure of oral TBPM-PI-HBr administered in a fasting or fed state (Study 994-101, described in the Investigator's Brochure).

A dummy infusion of normal saline (0.9%) and dummy placebo tablets will be used to maintain the blind.

6.2.3. Timing of Dose Administration

Early delivery of antibiotic 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. Following the first dose of IP, a one-time dose adjustment (of the second dose only) of either oral or IV study drug administration is allowed, to align with site-specific medication dosing schedules. The dosing interval adjustment must be such that the next dose of oral study drug is administered a minimum of 4 hours after the preceding dose and a maximum of 8 (±0.5 h) hours after the preceding dose, and the next dose of IV study drug (if adjusted) must be administered within 4 hours of its planned dosing schedule. Additional doses may be adjusted within the protocol-defined window of ±30 minutes per dose.

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

6.2.4. TBPM-PI-HBr Dose Adjustments in Subjects with Moderate Renal Insufficiency (CrCl >30 to ≤50 mL/min)

Model-based simulations using Phase 1 PK data from normal healthy volunteers and subjects with renal impairment indicate that reduction in TBPM-PI-HBr dosage is required for subjects with moderate renal insufficiency (CrCl >30 to ≤50 mL/min); therefore, subjects with

moderate renal insufficiency randomized to receive TBPM-PI-HBr will receive an adjusted dose of 300 mg PO q8h (Table 1). The dose rationale for TBPM-PI-HBr in moderate renal insufficiency is provided in the Investigator's Brochure.

No dose adjustment is required for ertapenem in subjects with moderate renal insufficiency.

Renal function as estimated by CrCl will be assessed using the Cockcroft-Gault formula (Exclusion Criterion 4) using serum creatinine levels obtained at the local laboratory at screening (baseline) and throughout the study. Subjects in either treatment group with moderate renal insufficiency identified at baseline/enrollment or while on study therapy will receive TBPM-PI-HBr (or dummy placebo) dosed as a single tablet according to their randomization assignment.

Table 1: TBPM-PI-HBr Dosage Regimen by Estimated Renal Function Category.

Renal function category	CrCl (mL/min)	TBPM-PI-HBr Dosage	TBPM-PI-HBr (300 mg)/Placebo Administration
Normal or mild insufficiency	>50	600 mg PO q8h	Two tablets PO q8h (±0.5 h)
Moderate insufficiency	>30 to ≤50	300 mg PO q8h	One tablet PO q8h (±0.5 h)
Severe insufficiency	≤30	Excluded	Not applicable

Note: For subjects with moderate renal insufficiency who have a baseline/screening CrCl near the threshold of mild renal insufficiency (i.e., 45-50 mL/min) in whom the CrCl is expected to increase >50 mL/min over the first day of therapy (e.g., after IV fluid hydration), the Investigator may choose to administer TBPM-PI-HBr dosage of 600 mg as a single initial dose (followed by 300 mg PO q8h starting with the second dose), while reassessing the need for a dosage adjustment based on a subsequent CrCl assessment.

6.2.5. Monitoring of CrCl during Study Drug Therapy

Subjects with cUTI/AP are at risk for renal insufficiency and/or acute kidney injury; therefore, study subjects require frequent monitoring of their renal function while on antibiotic therapy in order to determine the need for a TBPM-PI-HBr dosage adjustment based on a change in renal function category at any time during the treatment period from baseline to last dose of study drug.

- **For subjects with CrCl >50 ml/min and presumed stable renal function**, serum creatinine (measured by the local lab) and CrCl should be assessed at least every 3 days and the necessary dosage adjustments made as outlined in Table 1 for any decrease in CrCl ≤50mL/min.
- **For subjects with CrCl >30 to ≤50 mL/min or subjects suspected to have fluctuating renal function**, serum creatinine (measured by the local lab) and CrCl should be assessed *at least once* daily from the time of first dose until the CrCl stabilizes (i.e., no change renal function category) over 3 consecutive daily

measurements in order to determine whether a dosage adjustment as outlined in Table 1 is necessary.

- **For all subjects:** If the CrCl changes to a value that falls within 5 mL/min of the threshold requiring a change in study drug dosing, the Investigator may choose to implement the dosage adjustment or continue to monitor the subject over the next 24 hours and reassess the need for a dosage adjustment based on a subsequent CrCl assessment.
- **Note**: Subjects with baseline CrCl ≤30 mL/min are excluded from the study (Exclusion Criterion 4). After randomization, if the estimated CrCl decreases to ≤30 mL/min during the treatment period, further dosing of study drug should be suspended and a repeat serum creatinine measurement and recalculated CrCl performed to verify the need for study drug discontinuation. If the repeated CrCl is ≤30mL/min, study drug should be discontinued.

If a post-baseline dosage adjustment is determined necessary, the Investigator should inform the pharmacist immediately so that the appropriate changes to study drug may be implemented with the next possible dose of oral study drug (TBPR-PI-HBr/placebo).

Estimated CrCl should be calculated every time a local laboratory assessment of serum creatinine is performed. Local laboratory assessments of serum creatinine are required in these subjects due to the time delay in obtaining results from the central laboratory.

Actual weight in kilograms (not ideal weight) is required for the CrCl calculation. If available, the weight obtained on the day of the serum creatinine 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 eCRF.

6.2.6. Dosing Interruptions, Incomplete Doses, and Missed Doses

All instances of noncompliance with the pre-specified dosage regimen (oral study drug dosed q8h [±0.5 h] and IV study drug dosed q24h [±0.5 h]) 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 dosing is interrupted or incomplete, no adjustment to the dosing schedule is required.

If dosing is missed for any reason, the next planned dose should be administered as quickly as possible at the time of discovery.

For missed oral study drug doses, if the next planned dose is administered *within* 4 hours of its intended dosing time, the remainder of the doses should be administered at the pre-planned q8h intervals (i.e., the previous q8h dosage interval should remain as scheduled). If the next planned dose is administered *after* 4 hours of its intended dosing time, the remainder of the doses should be administered in a new q8h regimen starting with the timing of the restarted oral study drug administration.

For missed IV study drug doses, if the next planned dose is administered *within* 12 hours of its intended dosing time, the remainder of the doses should be administered at the pre-planned q24h intervals (i.e., the previous q24h dosage interval should remain as scheduled). If the next planned dose is administered *after* 12 hours of its intended dosing time, the remainder of the doses should be administered in a new q24h regimen starting with the timing of the restarted IV study drug administration.

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

6.2.7. Blinding the Treatment Assignment

This is a randomized, double-blind, double-dummy study; therefore, access to treatment allocation will be limited to unblinded members of the study team only. 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.

6.2.8. Allocation of Subjects to Treatment

Once informed consent has been obtained and eligibility has been determined, site personnel will obtain a subject number from a computer-generated randomization scheme using an interactive response technology (IRT). Subjects will be identified by a unique ten-digit subject identifier (e.g., 301-XXX-ZZZZ) in which the first three digits indicate the study identifier (e.g., 301), the second three digits indicate the site number, and the final four digits indicate the number assigned at randomization. For example, the first subject randomized at site 001 will be identified by the number 301-001-0001. Spero Therapeutics, Inc. will assign site numbers.

Randomization to treatment arms will occur in a 1:1 ratio. For this study, enrollment is considered to occur at the time a subject is randomized. Once a randomization number has been assigned, that number must not be used again if, for example, a subject 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 arms, the randomization will be stratified by type of infection and age of the subject at informed consent as follows:

Baseline Diagnosis

- AP
- cUTI

Age Group

- ≥18 to <65 years
- ≥65 years

6.2.9. Unblinding the Treatment Assignment

Data that may potentially unblind the treatment assignment (e.g., IP serum concentrations, treatment allocation, and IP preparation/accountability data) will be handled with special care during the data cleaning and review process. These data points will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. In the case of the blinded PK analysis of the first approximately 35 TBPM-PI-HBr subjects (among the first approximately 70 subjects enrolled), a masked data transfer will be sent to a blinded, independent PK Data Review Committee. 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 treatment assignment must not be broken during the study except in emergencies where the identification of the IP is required for further treatment of the subject.

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 IWRS and the source documents. After breaking the blind and the subject is withdrawn from the study, he or she should receive follow-up for safety purposes. Any code-breaks that occur must be reported to Spero Therapeutics, Inc. or its designee. Code-break information is held by the pharmacist or designated person at the site and by the CRO Medical Monitor for the study or designee.

6.3. Labeling, Packaging, Storage, and Handling

6.3.1. Labeling

Labels containing study information and packing identification will be handled via Spero Therapeutics, Inc.

Space is allocated on the label so that the site representative can record a unique subject identifier. Additional labels (e.g., those used when dispensing marketed product) may be applied, in certain cases, to the IP in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Identify the study subject by name
- Obscure the clinical study label

Additional labels may not be added without the Sponsor’s prior full agreement in advance.

6.3.2. Packaging

IP is packaged via Spero Therapeutics-approved vendors. Any changes to Sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the Sponsor.

6.3.3. Storage

TBPM-PI-HBr 300 mg film-coated tablets are packaged in 75cc white round high-density polyethylene bottles; 30 tablets/bottle and are stable after storage under accelerated conditions at 40°C/75% relative humidity for 3 months (supported by data generated on SPR994-101 GMP batch). Tablets are dispensed in a sealed, light-resistant container. The IPs must be stored as labeled in a secure area with access limited to the Investigator and authorized staff. IP supplies will be stored securely under the appropriate conditions according to local standard operating procedures. The Investigator has overall responsibility for ensuring that IP is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Temperature monitoring is required at the storage location to ensure that the IP is maintained within an established temperature range. 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 excursions on the IP and will provide supportive documentation as necessary. Under no circumstances should any product be dispensed to subjects until the impact is determined and deemed appropriate for use by the Sponsor.

6.3.4. Handling

The Sponsor will provide a sufficient quantity of IP supplies to each study site. Study sites must ensure that a responsible person correctly receives deliveries of IPs from the Sponsor, that all receipts of drug shipments are recorded on the appropriate drug accountability forms, and that the products are stored in a secure area under recommended storage conditions. It is also the responsibility of the Investigator to ensure that the integrity of packaged IPs not be jeopardized prior to dispensing. Only participants enrolled in the study may receive the IPs, in accordance with all applicable regulatory requirements. Only authorized and trained site staff may supply or administer the IPs.

An authorized and trained staff member at each study site will dispense the IPs according to pre-defined drug dispensing requirements. A second member of staff will verify the dispensing and administration. The staff member, not associated with any study assessments, will be responsible for dispensing study treatment in accordance with the randomization schedule. Individual doses will be dispensed by the pharmacy staff member on site the day of dosing and recorded in the drug accountability records. A study pharmacy manual will be prepared to define the procedures for dispensing.

6.4. Investigational Product Quality Complaints

Investigators are required to report IP quality complaints to Spero Therapeutics, Inc. within 1 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).

6.5. Drug Accountability

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

The Investigator has overall responsibility for administering IP. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form.

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

No IP 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 packaging are to be sent to a nominated contractor on behalf of the Sponsor. IPs 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 IPs must be packed in a tamper-evident manner to ensure product integrity. Contact the Sponsor for authorization to return any IP prior to shipment. Shipment of all returned IP 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 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 IPs 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 IPs delivered with those used and returned. All IPs 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 IPs will be described in the drug distribution plan.

6.6. Subject Compliance

Trained clinical facility personnel will facilitate and observe the administration of the IPs. The clinical facility personnel will record the exact dose and time of infusion.

Drug accountability must be assessed at the container/packaging level for unused IP 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.

7. STUDY PROCEDURES

7.1. Study Schedule

See Appendix 1 Schedule of Assessments.

The duration of study participation for each subject is approximately 30 days.

7.1.1. Screening Visit

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 assessments performed at the site within the Screening period (within 24 hours of randomization) may be used to determine subject eligibility even if performed prior to signing the informed consent form (ICF). For example, the Schedule of Assessments Table (Appendix 1) notes that "urine cultures collected per standard-of-care up to 24 h prior to randomization may be used for eligibility" (footnote j). Other routine clinical assessments may be used to determine eligibility if performed prior to informed consent but within the 24-hour Screening period.

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

- Physical exam and vital signs
- cUTI/AP symptoms and signs
- Local serum creatinine and calculated CrCl
- Urine culture collection
- Blood culture collection (if analysis is to be performed by the local laboratory rather than a regional laboratory)

Study SPR994-301-specific assessments, such as triplicate electrocardiograms, 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.

7.1.2. Treatment Visits

Treatment Visits, Day 1 up to Day 14: Subjects receive study drug (TBPM-PI-HBr or ertapenem) and dummy infusions or dummy tablets during this treatment period. The first treatment with the study drug may occur on the same calendar day as the Screening Visit. Day 1 is the first day of study drug administration. The duration of study drug therapy will be 7-10 calendar days; however, if the subject has a positive Screening or Day 1 blood culture for uropathogen growth, the duration of study drug therapy may be extended to up to a maximum of 14 calendar days at the discretion of the Investigator.

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 Schedule of Assessments, as Day 1 ECGs are timed from the first dose of study drug.

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
- 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
- *Separate Screening and Day 1 ECGs must be performed.* For Screening ECGs, perform 12-lead ECGs in triplicate at 1-5 minute intervals (calculate mean QTcF value for eligibility). For Day 1 ECGs, perform 12-lead ECGs in triplicate at 1-5 minute intervals 1h (±15 min) after the first oral dose administration.

7.1.3. End-of-Treatment Visit

The EOT Visit will be completed on the last day of study drug administration (Day 7-10, or up to Day 14 for bacteremic subjects), or the following day (e.g., allowing a one-day window to complete procedures with the exception of EOT ECGs which must be performed one hour (±15 min) after the last dose rather than the following day). Decision on treatment completion should be made by the Investigator based on his/ her clinical judgment (e.g., complete resolution or significant improvement of signs and symptoms of cUTI/AP that were present at baseline with no need for further antibiotic treatment). Subjects requiring more than 10 days of treatment (or more than 14 days of treatment for bacteremic subjects) will be discontinued from the study drug. These subjects will be assessed at EOT as clinical and microbiological failures, and treated with an appropriate open-label antibiotic at the discretion of the Investigator. The subjects will remain in the study for the remaining visits.

7.1.4. Test-of-Cure Visit

The TOC Visit is Day 19 (± 2) for all subjects.

7.1.5. Late Follow-Up Visit

The LFU Visit is Day 25 (± 2) for all subjects.

7.1.6. Additional Care of Subjects after the Study

No after care is planned for this study.

7.2. Study Evaluations and Procedures

7.2.1. Efficacy

Efficacy will be evaluated through assessment of clinical outcomes, microbiological culture, and susceptibility testing of bacterial isolates. Measures of clinical efficacy will be assessed at baseline and at multiple time points during the study.

Overall response (combined clinical cure plus microbiological eradication) at TOC will be assessed in the micro-ITT population, 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 antimicrobial therapy is warranted and subject is alive
- Microbiological eradication is defined as a reduction of baseline urine pathogen(s) to $<10^3$ CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at baseline and subject is alive

Subjects prematurely discontinued from IP for safety reasons and who require further antibacterial therapy for the cUTI/AP should be assessed as a clinical and microbiological failure at EOT and TOC.

7.2.1.1. Investigator Assessment of Clinical Outcomes

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: Subject 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 antimicrobial therapy is warranted
- 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 subject is a cure or failure

Subjects 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.

Based on the assessment of signs and symptoms, the Investigator will choose one of the following clinical outcomes at the LFU Visit:

- Sustained clinical cure: Met criteria for clinical cure at TOC, and remained free of signs and symptoms of cUTI or AP at LFU Visit

- Clinical relapse: Met criteria for clinical cure at TOC, but new signs and symptoms of cUTI or AP are present at the LFU Visit and the subject requires antibiotic therapy for the cUTI
- Clinical indeterminate: Insufficient data are available to determine if the subject is a sustained clinical cure or clinical relapse

Note: If a subject is assessed as a clinical failure at EOT, the subject is automatically considered a failure at the TOC and LFU Visits, and an assessment of clinical response by the Investigator will be listed as "failure at EOT."

7.2.1.2. Microbiologic Outcomes

Per-subject microbiological response at the EOT and TOC visits is determined programmatically based on the results of blood and urine cultures as one of the following outcomes:

- Microbiologic eradication: Subject is alive and all baseline uropathogen(s) are reduced to $<10^3$ CFU/mL on urine culture and negative on repeat blood culture (if positive at baseline)
- Microbiologic persistence: Isolation from urine culture of $\geq 10^3$ CFU/mL or from blood of any of the baseline uropathogen(s) identified at study entry; subjects with a microbiologic persistence outcome at EOT will be considered a persistence at TOC
- Microbiologic indeterminate: No follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason, or the follow-up urine culture is considered contaminated

Per-subject microbiological response at the LFU visit is determined based on outcomes at the TOC visit and subsequent blood and urine cultures as one of the following outcomes:

- Sustained microbiologic eradication: Microbiologic eradication at the TOC and no subsequent urine culture after TOC demonstrating recurrence of the original baseline uropathogen at $\geq 10^5$ CFU/mL
- Microbiologic recurrence: Isolation from urine culture at $\geq 10^3$ CFU/mL or blood culture of any of the baseline uropathogen(s) at any time after documented eradication at the TOC Visit up to and including the LFU visit
- Microbiologic indeterminate: No follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason, or the follow-up urine culture is considered contaminated

Additional microbiologic outcomes include the following:

- Colonization: Isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL (other than the original baseline pathogen[s]) from a urine culture in a subject who is assessed as a clinical cure or sustained clinical cure (e.g., requires no additional or alternative antimicrobial therapy)

- Superinfection: Isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL (other than the original baseline pathogen[s]) from a urine culture that is accompanied by clinical signs and symptoms of infection requiring alternative antimicrobial therapy (e.g., the subject is assessed by the Investigator as a clinical failure) during the period up to and including EOT
- New infection: Isolation of a new pathogen(s) at $\geq 10^5$ CFU/mL (other than the original baseline pathogen[s]) from a urine culture that is accompanied by clinical signs and symptoms of infection requiring alternative antimicrobial therapy (e.g., the subject is assessed by the Investigator as a clinical failure) in the time period after EOT

7.2.2. Microbiological Assessment

Microbiological assessment will be performed with urine cultures, blood cultures, and rectal swabs. 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.

Local or regional microbiology laboratory sample processing, including isolate identification and quantification, will be used to help guide clinical care and support Investigator assessments. Local or regional laboratory susceptibility testing, if available, will be performed per local standards. The Central Microbiology Laboratory will be used for evaluating isolate(s), identification, and antimicrobial susceptibility testing; Central Microbiology Laboratory data will be used for microbiologic outcome determinations.

7.2.2.1. Urine Cultures

Urine specimens for culture will be obtained at the Screening, Day 5, EOT, TOC, and LFU Visits and, in addition, as clinically indicated throughout the study. At LFU, urine culture must be obtained only in subjects with a positive urine culture (growth of urine culture bacterial pathogen(s) $\geq 10^5$ CFU/mL) on or after the TOC Visit. In addition, at any time the subject is deemed a clinical failure, a urine specimen should be obtained for culture prior to the start of any rescue antimicrobial therapy.

All urine culture specimens must be obtained through one of the following methods that minimizes the risk of bacterial contamination:

- Clean-catch mid-stream
- Newly-inserted Foley catheter (bag specimens are not permitted)
- Bladder needle aspiration
- Ureter aspiration

Urine specimens should be processed for culture by the local lab within 2 h of collection. If the local laboratory cannot process the sample within 2 h of collection, the sample may be stored at 4°C (during transport and holding period) for up to 24 h. If refrigeration is not

possible and specimens are delayed in transport and/or processing, the urine specimen should be collected in transport tubes with preservatives, as directed in a laboratory manual.

All Screening urine cultures will require the use of a 1 µL loop to obtain a $<10^5$ CFU/mL threshold; 1 µL loops will be provided by the Central Microbiology Laboratory. All Screening urine culture pathogens that grow at $\geq 10^3$ CFU/mL will be sent to the central laboratory. To be considered an eligible uropathogen for micro-ITT analysis, the baseline urine culture must grow 1 or 2 bacterial isolates, each at $\geq 10^5$ CFU/mL. If ≥3 bacterial isolates are identified, the culture will be considered contaminated, regardless of colony count, unless one of the organisms present in urine at $\geq 10^5$ CFU/mL comprises ≥80% of the total growth (predominant), or ≥1 of the organisms is cultured from a Screening or Day 1 blood culture.

All post-baseline cultures will require the use of a 1 µL loop and a 10 µL loop to obtain a $<10^3$ CFU/mL threshold; 1 µL loops and 10 µL loops will be provided by the Central Microbiology Laboratory. For post-baseline urine cultures, all isolates that grow $\geq 10^3$ CFU/mL will be sent to the central laboratory. Culture results are to report pathogen identification to the species level.

Susceptibility testing for TBPM-PI-HBr will not be available to the local laboratory; however, TBPM-PI-HBr susceptibility will be assessed at the Central Microbiology Laboratory by MIC and disk method. These centrally-determined susceptibility results will not be available to the Investigator during real-time management of the subjects; therefore, decisions related to subject care (e.g., study drug discontinuation) will be based on the evolution of the clinical signs and symptoms of the index cUTI or AP, rather than specific TBPM-PI-HBr susceptibility data. Susceptibility testing for carbapenems (e.g., ertapenem) can be performed locally using routine standard materials and methods by the laboratory. Results of this testing can be used by Investigators along with clinical findings to help guide therapy. When local susceptibility testing suggests non-susceptibility to study drug (e.g., intermediate susceptibility or resistance to ertapenem) but the subject is stable or clinically improving, the subject should remain on the study drug at the Investigator's discretion. Such cases should be discussed with the Medical Monitor prior to study drug discontinuation.

With the exception of the "contaminants" listed below, all isolates from urine cultures that grow $\geq 10^3$ CFU/mL are to be sent to the Central Microbiology Laboratory. The Central Microbiology Laboratory will reculture the shipped isolates, confirm genus and species identification, and determine pathogen susceptibility by standardized broth microdilution and disk diffusion methods for TBPM-PI-HBr and ertapenem. In the event that local laboratory genus and species identification are not consistent with central laboratory results, a back-up isolate should be sent to the Central Microbiology Laboratory.

For the purposes of this study, the following organisms are considered "contaminants" and should not to be sent to the Central Microbiology Laboratory:

- Non-group D streptococci (e.g., any streptococcal species with the exception of Lancefield Group D streptococci; examples of Group D streptococci include *Streptococcus bovis, S. equinus, S. gallolyticus, S. pateuriaus, S. infantarius, S. lutetiensis*)

- Coagulase-negative staphylococci with the exception of *Staphylococcus saprophyticus* (e.g., *S. epidermidis, S. haemolyticus, S. hominis*)
- Corynebacterium spp. with the exception of *Corynebactrium urealyticum*
- *Lactobacillus* spp.
- *Propionibacterium* spp.
- Yeast (e.g., *Candida* spp.)

Refer to the study-specific laboratory manual for further detail, including specific procedures pertaining to the collection, processing, storage, and shipment of microbiological samples.

7.2.2.2. Blood Cultures

At Screening, two sets of blood cultures (i.e. one aerobic blood culture bottle and one anaerobic 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 uropathogen). 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 TBPM-PI-HBr will not be available to the local laboratory; TBPM-PI-HBr susceptibility will be assessed at the central laboratory. Therefore, decisions related to subject care (e.g., study drug 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.

7.2.2.3. Rectal Swab Samples

Rectal swab samples for antibiotic-resistant *Enterobacteriaceae* culture will be obtained prior to randomization and at TOC. Additional detail is available in the laboratory manual.

7.2.2.4. Central Microbiology Laboratory Procedures

With the exception of "contaminants" defined above, all isolates from urine cultures that grow $\geq 10^3$ CFU/mL and all bacterial isolates from blood cultures collected at each defined visit will be shipped to the designated Central Microbiology Laboratory from each study site. The Central Microbiology Laboratory will confirm the identity of all bacterial isolates to the genus and species level and perform susceptibility testing against all bacterial isolates for TBPM-PI-HBr and ertapenem using standardized susceptibility testing methods.

Any questions regarding microbiological procedures, interpretation of results, or storage of isolates should be discussed with the Sponsor or designee. Additional detail is available in the laboratory manual.

7.2.3. Safety

7.2.3.1. Medical/Surgical and Medication History

The medical/surgical history of the subject 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, gastrointestinal/hepatic, genitourinary/renal, neurologic, and psychiatric/psychosocial.

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

History of prior 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 subject's source documents and on the medical history CRF. Height and weight will be taken during this physical exam. Complete physical examinations at Screening, EOT, TOC, and LFU consist of skin, head and neck, heart, lung, abdomen, extremities, back/flank/costovertebral angle tenderness, and neuromuscular assessments. Limited physical examinations between Day 1 and EOT are focused, 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.

7.2.3.3. Adverse Event Collection

At each study visit, subjects 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?"). AEs will be collected from the time of the first dose of IP.

7.2.3.4. Vital Signs

Vital sign assessments include blood pressure, pulse, respiratory rate, and temperature. 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), TOC, and LFU. If the Screening Visit and Day 1 occur on the same calendar day, repeated vital signs on Day 1 are optional. 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 subject'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 clinically significant deviations from baseline vital signs, which are deemed clinically significant 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 clinically significant (NCS) or clinically significant (CS). Abnormal clinical laboratory values, that are unexpected or not explained by the subject's clinical condition may be, at the discretion of the Investigator or Sponsor, explained or resolved as soon as possible.

Laboratory Assessments for Eligibility

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), 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, Day 3, Day 5, Day 7, Day 9 (if still receiving IP), Day 11 (if still receiving IP), Day 13 (if still receiving IP), EOT, TOC, and LFU.

- Hematology (hemoglobin [Hb], hematocrit, red blood cell [RBC] indices)
- Thrombocyte count (platelets)
- Reticulocyte count
- White blood cell count with differential (including neutrophils, eosinophils, basophils, lymphocytes and monocytes)
- Coagulation (prothrombin time, international normalized ratio, thrombin time, activated partial thromboplastin time)
- Serum Chemistry:
  - Electrolytes (sodium, potassium, chloride, bicarbonate)
  - Non-fasting glucose
  - Blood urea nitrogen (BUN)
  - Creatinine (including calculated creatinine clearance (CrCl) using Cockcroft-Gault formula)

  - L-carnitine
- Creatine kinase
- Urate
- Phosphate
- Total calcium
- Cholesterol
- Albumin
- Globulins
- 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 include WBC, RBC, epithelial cells and bacteria testing.

7.2.3.6. Pregnancy Test

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.

In addition, a serum β-HCG pregnancy test is performed by the central laboratory on all FOCP at the Screening Visit and at the subject's final visit (LFU Visit or time of early withdrawal from the study) (Appendix 1).

7.2.3.7. Electrocardiograms

At Screening, perform 12-lead ECGs in triplicate at 1-5 minute intervals. On Day 1, perform 12-lead ECGs in triplicate at 1-5 minute intervals 1h (±15 min) after the first oral dose administration. At EOT, perform 12-lead ECGs in triplicate at 1-5 minute intervals 1h (±15 min) after the final oral dose administration. At TOC, perform a single 12-lead ECG.

7.2.4. Pharmacokinetics

7.2.4.1. Blood Sample for Plasma Pharmacokinetics

Blood samples will be collected for assessment of PK parameters for TBPM-PI-HBr. Refer to the laboratory manual for detailed instructions on sample processing, storage, and shipping. Blood samples include:

Sentinel PK Analysis Group: First approximately 35 TBPM-PI-HBr-treated subjects among the first approximately 70 subjects enrolled.

- Plasma PK Assessments: Blood samples will be collected following an oral dose (first, second, or third) on Day 2 at the following time intervals after oral administration of study drug: 0.25 h (± 5 min); 0.5 h (± 5 min); 1 h (±15); 2 h (±15); and 8 h (±15 min but prior to the next scheduled dose). These samples will be used to estimate PK parameters, such as AUC, C_{max}, T_{max}, CL, $t_{1/2}$, C_{min}, and V_{SS}

Sparse PK Analysis Group: For all subjects enrolled after the first approximately 70 subjects enrolled.

- Plasma PK Assessments: Blood samples, using sparse sampling (3 samples/subject), will be collected following an oral dose (first, second, or third) on Day 2 of treatment at the following time intervals after oral administration of study drug: 1 h (±15 min), 4 h (±1 h); and 8 h (±30 min but prior to the next scheduled dose).

Whole blood samples will be assayed by validated liquid chromatography tandem mass spectrometry (LC/MS/MS) methods, which are specific for the determination of TBPM. Blood samples will be collected from all subjects. Only samples from subjects who receive a dose of TBPM-PI-HBr will be analyzed. 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.

When collecting PK blood samples for both the Sentinel and Sparse PK Analysis Group, the exact dose time and the exact PK sample time should be collected.

The validation study conducted by the appointed bioanalytical laboratory to establish validity including accuracy, precision, reproducibility, specificity, recovery and frozen stability of the analytical method will be appended to the final report.

7.2.4.2. Urine Collection for Pharmacokinetics

For the first approximately 70 subjects, a 24 h urine collection will be collected in roughly three (3) 8-h aliquots after the first dose of the study drug on Day 1. These collections should occur as close as possible to the 8 hour time limit. Deviations will only be documented for those collections that occur outside of a 7-9 hour window.

7.2.5. Volume of Blood to be Drawn from Each Subject

During this study it is expected that blood will be taken from all subjects, regardless of sex. Exact blood volumes to be drawn can be found in the study lab manual.

7.2.6. Other Tests

7.2.6.1. Urinary Tract Instrumentation Status

Record all start times and end times of all urinary tract instrumentation, including but not limited to bladder catheters, stents, nephrostomy tubes, and other urological prosthetic material.

7.2.6.2. Site of Care

Record the site of care (e.g., acute care hospital ward, long-term care facility [US only]), outpatient infusion center (US only).

8. ASSESSMENT AND MANAGEMENT OF ADVERSE EVENTS

8.1. Adverse Event Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a subject 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 subject 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 Principal Investigator. For the purposes of this study, duration of intended hospitalization at the time of study randomization may be reasonably presumed to be approximately 14 days, as this is the maximum allowed duration of study drug. Therefore, cases of clinical failure leading to prolongation of hospitalization beyond approximately 14 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 adverse event (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 serious adverse event (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 subject/event outcome or action criteria described above and is usually associated with events that pose a threat to a subject'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):** An AE or suspected adverse reaction is considered "unexpected" if:

- It is not listed in the Investigators Brochure
- It is not listed at the specificity or severity that has been observed
- The IB is not required or available or not consistent with the risk information described in the general investigational plan or elsewhere in the current application

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

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 **CS** 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 AEs and SAEs

8.2.1. Assessment of Intensity

The Principal Investigator (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 subject, 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 subject 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 subject signed the informed consent
- **Recovering/Resolving:** This term is only applicable if the subject has completed the trial or has died from another AE. The condition is improving and the subject is expected to recover from the event
- **Recovered/Resolved with sequelae:** The subject 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 subject 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 subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject 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 subject is lost to follow-up

8.2.2. Assessment of Causality

The PI (or designee) will make an assessment as to the relationship between IP and the occurrence of each AE/SAE. The PI (or designee) will use clinical judgment to determine whether or not the AE/SAE is causally related to the IP. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP will be considered and investigated. The PI (or designee) will also consult the IB in the determination of his/her assessment.

The causal relationship of the study drug to an AE will be rated 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 subject'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 subject'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

There may be situations when an SAE has occurred and the PI (or designee) has minimal information to include in the initial report to the Sponsor. However, it is very important that the PI (or designee) always make an assessment of causality for every event, prior to transmission of the SAE form to the Sponsor. The PI (or designee) may change his/her opinion of causality in light of follow-up information, amending the SAE form and the CRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The PI (or designee) will provide an assessment of causality as per instructions on the SAE form.

8.3. Time Period, Frequency and Method of Detecting AEs

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 IP will be documented as Medical/Surgical History.

Any medical occurrence reported or observed after the first dose of IP 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 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 subject 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 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 subject'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 subject 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 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.

The PI (or designee) is responsible for notifying the local IRB, local IEC, or the relevant local regulatory authority 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 subject, he/she will report the information to the Sponsor (or delegate) and Medical Monitor within 24 hours. 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 designated time frames. 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.

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 Representative or emergency contact.

AEs will be classified as SUSARs if the AE or suspected adverse reaction meets the definition of "unexpected" in Section 8.1. SUSARs should be reported to the Ethics Committees and to the Regulatory Authority in accordance with applicable regulatory requirements for expedited reporting. It is the Investigator's responsibility to report SUSARs to the Ethics Committee and Regulatory Authority.

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 participants. 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 IP, 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 subject and provide further information to the Sponsor on the subject's condition.

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 subject 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 subject 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 subjects 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.

8.8. Clinical Laboratory Evaluations

A change in the value of a clinical laboratory assessment can represent an AE if the change is clinically relevant or if, during treatment with the IP, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the EOT with the IP, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values, which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal clinical laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory parameter is CS, and therefore represents an AE.

8.9. Pregnancy

Any report of pregnancy for any female study subject or male study subject's partner must be reported within 1 business day to the CRO. The female study participant must be withdrawn from the study.

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.

In addition, a serum β-HCG pregnancy test is performed by the central laboratory on all FOCP at the Screening Visit and at the subject's final visit (LFU Visit or time of early withdrawal from the study) (Appendix 1).

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.

Pregnancy outcomes should be collected for female partners of any males who took the IP if possible. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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 HCG test or ultrasound result will determine the pregnancy onset date.

8.10. 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 1 business day reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

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

- **Abuse:** Persistent or sporadic intentional intake of IP 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 an IP (For studies, medication errors are reportable to the Sponsor)
- **Misuse:** Intentional use of IP other than as directed or indicated at any dose (*Note:* this includes a situation where the IP is not used as directed at the dose prescribed by the protocol)
- **Overdose:** Intentional or unintentional intake of a dose of an IP exceeding a pre-specified total daily dose of the product

Cases of subjects missing doses of product are not considered reportable as medication errors.

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 IP, including use of appropriate diluent and the timeframe in which IP is to be used after reconstitution and/or dilution, are reportable as medication errors.

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

8.11. Serious Adverse Event Procedures

8.11.1. Reference Safety Information

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

The reference for safety information for the comparator in this study is the ertapenem SmPC/Product Package Insert, which the Sponsor has provided separately to all Investigators.

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

The Investigator is responsible for notifying the local IRB, local IEC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1. Data Collection

The Investigators' authorized site personnel must enter the information required by the protocol on the CRF. A Study Monitor 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.

9.3. Statistical Analysis Process

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 or to the data to be collected from a subject, 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 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 9.10.1; 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 study drug.

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

9.4. Planned Interim Analysis, Adaptive Design, Sponsor Data Review Committee, and Data Safety Monitoring Board

Masked individual and composite PK data from the first approximately 35 TBPM-PI-HBr subjects enrolled (among the first approximately 70 total subjects enrolled) will be reviewed by a blinded, independent PK Data Review Committee to verify the TBPM-PI-HBr dose. This review will be blinded and will only be a review of PK data; this is not a formal review of either safety or efficacy. PK samples obtained from the TBPM-PI-HBr group will be analyzed using a validated assay by a central bioanalytical laboratory. Study enrollment will continue uninterrupted during this blinded interim PK data assessment, and the remaining subjects will undergo sparse PK sampling. If TBPM-PI-HBr dose alteration needs to be considered, enrollment may be paused for sample size adjustment and protocol amendment. If a change in dose is required, the planned total enrolment may be adjusted as needed to ensure sufficient data are available from 884 evaluable subjects receiving the amended dose (Section 9.13).

A blinded sample size reassessment will take place after 70% of the subjects have response data at TOC available and will be performed by the blinded Sponsor Data Review Committee (DRC). The blinded sample size re-estimation will either confirm the initial sample size estimate is adequate or increase the sample size (number of randomized subjects) to ensure the study has adequate power for the primary outcome measure, up to a maximum of 1,450 subjects. In addition, the sample size may be increased based on a lower than expected evaluability rate (the proportion of randomized subjects included in the microbiological ITT population). No sample size adjustment downwards will be performed.

The sample size re-estimation will be based on a blinded review of the overall response rate and evaluability rate according to pre-specified criteria documented in a sample size reassessment document (DRC Charter).

No alpha adjustment will be made as this will be a blinded reassessment and no treatment group comparison will be performed for any endpoint.

A DSMB will be involved in the management of this study to review safety. The DSMB will review safety data upon enrollment of 25% and 50% of subjects. Full details regarding the DSMB (e.g., committee composition, the criteria for scheduling an ad hoc meeting, what will be presented/decided) will be specified in the DSMB charter. The DSMB charter will be approved and finalized by the DSMB members prior to the first DSMB meeting.

9.5. Selection of Subjects to be Included in the Analyses

Intent-to-Treat (ITT) Population: All subjects who were randomized, regardless of whether they received any study drug. Subjects will be summarized by treatment to which they were randomized.

Safety Analysis Population: Randomized subjects who received any amount of study drug. Subjects will be summarized by treatment to which they received.

Microbiological Intent-to-Treat (micro-ITT) Population: All randomized subjects with a confirmed diagnosis of cUTI or AP (Inclusion Criterion 4) and a positive Screening urine culture defined as growth of one or two uropathogens at $\geq 10^5$ CFU/mL. Subjects with

Screening urine culture growth of more than 2 species of microorganisms will be excluded from the micro-ITT Population, regardless of colony count. Any subject with cUTI or AP caused by a pathogen that is typically not expected to respond to either carbapenem study drug (e.g., *Acinetobacter* spp., *Stenotrophomonas* spp., *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* [MRSA]) will also be excluded from this population.

Clinically Evaluable (CE) Population: Subjects who meet the definition for the ITT population, have no important protocol deviations that would affect the assessment of efficacy (to be defined in the SAP), and had an outcome assessed as clinical cure or clinical failure at EOT, TOC, and/or LFU.

Microbiologically Evaluable (ME) Population: Subjects who meet the definitions of both the micro-ITT Population and CE Population.

Pharmacokinetic (PK) Population: All subjects treated with at least one dose of TBPM-PI-HBr with at least one analyzable plasma or urine PK sample.

9.6. Subject Disposition

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

9.7. 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 ITT and Safety Analysis population. Demographic and baseline disease characteristic data will also be listed.

9.8. Investigational Product Exposure

The number of subjects receiving TBPM-PI-HBr and ertapenem, the planned and total doses received, and along with the duration of exposure, will be summarized by treatment groups in the study for all subjects in the Safety Analysis population.

9.9. Prior and Concomitant Medication

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

Prior treatment includes all treatment (including OTC treatments such as herbal treatments, vitamins, diet aids, hormone supplements; and non-pharmacological treatment such as psychotherapy, as appropriate) received within 30 days (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) of and discontinued prior to the date of first dose of IP.

Prior and concomitant medications will be listed and summarized by preferred drug name and treatment group for the ITT and Safety Analysis population. See Inclusion/Exclusion criteria.

9.9.1. Prohibited Concomitant Medications

Treatment with any of the following concomitant medications or procedures is prohibited:

- Any additional or adjunctive, non-study-specific, antibacterial drug therapy (between randomization and LFU) that would potentially effect outcome evaluations of cUTI/AP, except in cases of clinical failure of study drug therapy for the index cUTI/AP, including but not limited to systemic antibacterials with potential activity vs. uropathogens (e.g., *Enterobacteriaceae*), antibacterial drug prophylaxis, and antibacterial bladder irrigation
- Gastric acid-reducing medications (between randomization and EOT), including but not limited to proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole), histamine-2 receptor antagonists (e.g., nizatidine, famotidine, cimetidine, ranitidine), and antacids (e.g., Alka-Seltzer, Milk of Magnesia, Amphojel, Gelusil, Maalox, Mylanta, Rolaids, Pepto-Bismol)
- Valproic acid or divalproex sodium (between randomization and EOT)
- Probenecid (between randomization and EOT)

9.9.2. Permitted Concomitant Medications

With the exception of prohibited concomitant medications discussed above (Section 9.9.1), other concomitant medications are permitted. For example, the following concomitant medications are permitted:

- Antibiotics for the treatment of *C. difficile* (e.g., metronidazole, oral vancomycin, fidaxomicin)
- Antiemetics, including but not limited to: 5-HT_3 receptor antagonists (e.g., ondansetron, mirtazapine, dolasetron), dopamine antagonists (e.g., olanzapine, droperidol, domperidone), NK1 receptor antagonists (e.g., aprepitant, rolapitant), antihistamines (e.g., diphenhydramine, dimenhydrinate, promethazine), and anticholinergics (e.g., hyoscine)
  - Note that concomitant gastric acid-reducing medications are prohibited (Section 9.9.1) and should not be used to alleviate nausea or vomiting
- Topical antibiotics other than those used for bladder irrigation
- Antibiotics for the treatment of infections other than cUTI/AP that do not have a gram-negative spectrum of activity. For example, agents with Gram-positive only coverage (e.g., vancomycin, daptomycin, or linezolid) for suspected or identified carbapenem-resistant Gram-positive pathogens may be considered.
  Administration of non-study antibacterials for reasons other than clinical

failure of study drug for the index cUTI/AP requires approval by the Medical Monitor.

9.10. Efficacy Analyses

9.10.1. Primary Efficacy Variables

Overall response (combined clinical cure plus microbiological eradication) at TOC in the micro-ITT population, 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 antimicrobial therapy is warranted and subject is alive
- Microbiological Eradication is defined as a reduction of baseline urine pathogen(s) to $<10^3$ CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at baseline and subject is alive

Subjects prematurely discontinued from IP for safety reasons and who require further antibacterial therapy for the cUTI/AP should be assessed as a clinical and microbiological failure at EOT and TOC. Subjects who are prematurely discontinued from IP administration due to insufficient therapeutic effect should be assessed as clinical and microbiological failure at EOT and automatically assigned an outcome of clinical and microbiological failure at TOC.

For the overall response, subjects 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 response to either clinical cure, microbiological eradication, or both) at TOC. Subjects 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, subjects with an indeterminate outcome will be considered failures for the primary analysis. The number and percentage of subjects 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 TBPM-PI-HBr group,

P2 = overall responder (success) rate in the ertapenem group,

Δ = the non-inferiority margin

The non-inferiority hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. The 95% CI will be calculated using the method of Mietennen and Nurminen. If

the lower limit of the 95% CI for the difference in overall response is greater than -12.5%, non-inferiority will be declared.

The primary efficacy data will also 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.

As outlined in Section 9.13.1, in the setting of the ongoing COVID-19 pandemic, the statistical analyses and assessment of non-inferiority for the primary endpoint were revised in consultation with the US FDA, in order to preserve data integrity and to ensure the safety of patients and study team by limiting further enrollment into the study. The justification for this NI margin is provided in the June 2018 (Revision 1) FDA Guidance "Complicated Urinary Tract Infections: Developing Drugs for Treatment". This guidance demonstrates that the benefit of active antibacterial therapy over no treatment (M1) is estimated to be 30%. Therefore, an NI margin of -12.5% is deemed appropriate given the proposed margin is well below the M1 of 30% and retains greater than 50% of the clinical benefit (M1), whilst comparing TBPM-PI-HBr to an IV carbapenem comparator.

9.10.2. Secondary Efficacy Variables

Secondary Variables include:

- Overall response (combined clinical cure plus microbiological eradication as defined above) at the TOC Visit in the ME population
- Clinical cure at EOT, TOC, and LFU Visits in the micro-ITT, CE, and ME populations
- By-subject and by-pathogen microbiological eradication at EOT, TOC, and LFU in the micro-ITT and ME populations
- Overall response in subgroups, including:
  - Stratified infection category
  - Stratified age category
  - Country/Region
- Time (days) to resolution or improvement of signs and symptoms of cUTI and AP present at baseline in the micro-ITT populations
- Time (days) to defervescence in micro-ITT subjects with a documented fever at Screening or Day 1
- Rate of clinical relapse at the LFU Visit in the micro-ITT population
- Rates of superinfection and new infection in the micro-ITT population
- Determine PK parameters (e.g., Vd, C_{max}, AUC, T>MIC) in TBPM-PI-HBr recipients in the PK population

9.10.3. Exploratory Efficacy Variables

Exploratory efficacy variables include:

- Enteric colonization with antibiotic-resistant *Enterobacteriaceae* at the TOC Visit in the micro-ITT population
- By-subject and by-pathogen microbiological eradication and clinical improvement at Day 5 in the micro-ITT, CE, and ME populations
- Clinical, microbiological, and overall responses at TOC among subjects with cUTI/AP caused by ESBL-producing *Enterobacteriaceae*

9.11. Safety Analyses

All safety analyses will be summarized and listed using the Safety Analysis 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 21.0. AEs will be recorded from the first dose of IP through LFU. TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of IP 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 IP 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 subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to study drug.

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 creatinine, 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.

9.12. Other Analyses

9.12.1. Pharmacokinetic Analyses

The PK population includes two sets of TBPM-PI-HBr-treated subjects, the Sentinel PK Analysis Group and the Sparse PK Analysis Group.

The Sentinel PK Analysis Group is the first 35 TBPM-PI-HBr-treated subjects among the first 70 subjects enrolled. Plasma and urine PK Assessments for this group will be performed as follows:

- Plasma PK Assessments: Blood samples will be collected following an oral dose (first, second, or third) on Day 2 at the following time intervals after oral administration of study drug: 0.25 h (± 5 min); 0.5 h (± 5 min); 1 h (± 15 min); 2 h (± 15 min); and 8 h (± 15 min but prior to the next scheduled dose); these samples will be used to estimate PK parameters, including $AUC_{0\text{-}t}$, AUC_{extrap}, $AUC_{0\text{-}oo}$, λz, Vd, T>MIC, C_{max}, T_{max}, CL, $t_{1/2}$, C_{min}, and V_{SS}
- Urine PK Assessments: Twenty-four (24) hour urine collection will be collected roughly in three (3) 8-h aliquots starting on Day 1; TBPM concentrations will be measured and total 8-h, 16-h and 24-h urine elimination will be estimated

The Sparse PK Analysis Group includes all subjects enrolled after the first 70 subjects.

- Plasma PK Assessments: Blood samples, using sparse sampling (3 samples/subject), will be collected following an oral dose (first, second, or third) on Day 2 of treatment at the following time intervals after oral administration of study drug: 1 h (± 15 min); 4 h (± 1 h); and 8 h (± 30 min but prior to the next scheduled dose)
- Urine PK Assessments will not be performed for this set of subjects

Pharmacokinetic parameters will be estimated for each subject sample. The following parameters will be derived for the sentinel PK group:

Parameter	Definition
C_{min}	The minimum observed concentration.
C_{max}	The maximum observed concentration.
T_{max}	The time at which C_{max} was apparent.
$AUC_{0\text{-}t}$	The area under the concentration versus time curve from time zero to the sampling time at the last quantifiable concentration (C_t) at the time of the last quantifiable concentration (t_{last}) calculated by the linear trapezoidal rule.
AUC_{extrap}	The area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of total AUC.
λ_z	The apparent terminal rate constant, estimated using the negative slope of the least square regression analysis of the log concentration versus time data for the terminal linear portion of the curve.

Parameter	Definition
$t_{1/2}$	The apparent terminal half-life, calculated from Ln 2 / λ_z.
$AUC_{0-¥}$	The area under the concentration-time curve estimated from time zero to infinity as the sum of the 2 areas: AUC_{0-t} and AUC_{extrap}, where AUC_{extrap} is calculated as C_t / λ_z.
CL	The systemic clearance calculated as: Dose/$AUC_{0-¥}$.
T>MIC	The time above the minimum inhibitory concentration.
Vd	The apparent volume of distribution, calculated as the amount of drug in the body divided by the concentration of drug in the blood/plasma.
V_{ss}	The apparent volume of distribution at steady state.

Additional PK parameters may be calculated as appropriate. A separate PK SAP will be written providing full details of the parameter estimations and PK analyses.

9.13. Sample Size Calculation and Power Considerations

The sample size was determined based on the primary endpoint of overall response. Planned enrollment for this study is approximately 1200 subjects.

Assuming a response rate of 70% for both treatment groups, a pre-specified NI margin of 10%, a 1:1 randomization ratio, and a one-sided significance level of 0.025, a trial including 884 evaluable subjects would have approximately 90% power to show NI within a 10% margin. This trial aims to recruit 884 subjects for inclusion in the micro-ITT population. Assuming 75% of randomized subjects are included in the micro-ITT population, approximately 1,180 subjects will be recruited to ensure 884 subjects in the micro-ITT population. This size study would also have 90% power for an analysis of the ME population, assuming a 75% response rate and 67% of randomized subjects are included in the ME population. A blinded assessment of overall evaluability rates (the proportion of randomized subjects in the micro-ITT and ME populations) and response rates (pooled across treatment groups) will be performed during the study, and if assumptions are very different to those expected the sample size may be increased up to a maximum of 1450 subjects according to pre-specified criteria (see Section 9.13 and 9.4 for details).

9.13.1. Changes Due to the COVID-19 Pandemic

At the time of the interim analysis (March 2020) the DRC performed the planned blinded sample size reassessment after response data at TOC was available for 70% of patients. Based on the preliminary review of blinded data, the DRC recommended continuing recruitment up to the protocol-allowed maximum of 1,450 patients (Section 9.4) in order to ensure inclusion of 884 eligible patients in the primary analysis population.

Based on the DRC recommendation, enrollment in the study continued, however the rate of enrollment dramatically decreased in the setting of the global COVID-19 pandemic and

related impact at multiple sites in countries where the study is being conducted. The Sponsor performed a continuous risk assessment in order to determine which sites could continue enrollment with minimal impact to patient/staff safety and post-treatment data collection. This ongoing risk assessment identified potential for significant impact to study conduct and data integrity based on difficulties in conducting post-treatment follow-up visits necessary for assessment of the primary endpoint, along with data monitoring of case records. Ultimately these challenges suggested that a progressively increasing proportion of indeterminate outcomes for the primary endpoint is likely with continued enrollment, which could bias the study towards non-inferiority. Therefore, the Sponsor, considered it in the best interest of the study, and study participants, to conclude enrollment and revise the planned analyses based on the available dataset.

Thus, as detailed in Section 9.10.1 , the original NI margin of -10% was modified to -12.5% in consultation with FDA. Based on this modification, it is expected that at least 670 patients will be included in the micro-ITT population, which ensures that the study will have >90% power to show non-inferiority when using a -12.5% NI margin assuming a true response rate of at least 60% across both treatment groups.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, International Council on Harmonisation (ICH), EU and its updates, and local ethical and legal requirements.

10.1. Sponsor's Responsibilities

10.1.1. Good Clinical Practice Compliance

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 GCP Guideline E6 (1996) and EU Directive 2001/20/EC.

Representatives of the study Sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, subjects' 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 regulatory authority 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 regulatory authority approvals required prior to release of IP for shipment to the site.

10.1.2. 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.

10.1.3. 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.

10.1.4. Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Independent Ethics Committees

The Sponsor will provide a summary of the Clinical Study Report within one year of the end of the study completion date to the competent authority of the Member State(s) concerned as required by regulatory requirement(s), and to comply with the community guideline on GCP. The Sponsor will provide the IECs with a copy of the same summary.

10.1.5. 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.

The Sponsor will make an end of study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC. End of study is the time at which all required data has been collected to answer the research question(s) in the protocol.

10.2. Investigator Responsibilities

10.2.1. Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC 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 subjects 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 subject has a primary care physician, the Investigator should, with the subject's consent, inform them of the subject's participation in the study.

10.2.2. 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 subjects 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 IP, 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 (inter)national 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.

10.2.3. Documentation and Retention of Records

10.2.3.1. Case Report Forms

Electronic Case Report Forms (eCRF) 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.

For electronic data capture studies the Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto 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.

10.2.3.2. 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 subject's medical file, subject diary cards, original clinical laboratory reports, and histology and pathology reports. All key data must be recorded in the subject's medical records.

The Investigator must 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 subject 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., subject'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 Food and Drug Administration [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.

10.2.3.3. 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 regulatory authorities), the EMA, other regulatory authorities, the Sponsor or its representatives, and the IRB/IEC for each site.

10.2.3.4. Financial Disclosure

Upon submission of a marketing application to the FDA for any drug, Spero Therapeutics, Inc. 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.

10.2.4. 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.

10.3. Ethical Considerations

10.3.1. Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study subjects prior to any study-specific procedures including Screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative is requested to sign the subject Informed Consent Form or a certified translation, after the subject has received and read (or been read) the written subject 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 subject's rights and responsibilities. A copy of the informed consent documentation (e.g., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the legally-authorized representative of the subject. If applicable, a consent form provided in a certified translation of the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

If subjects 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 subject Information and Consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

10.3.2. Institutional Review Board or Independent Ethics Committee

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 subject recruitment information to the IRB/IEC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an IEC opinion can be the Sponsor, the Investigator, or for multi-site studies the Coordinating PI or Sponsor, according to national provisions.

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 subject safety issue.

IP 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.

10.4. 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 (GDPR) 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 Spero Therapeutics, Inc. for 15 years. Use of individual subject data and/or remaining samples may result in patents or have other monetary value. These patents or other products resulting from subject samples/data will be owned by Spero Therapeutics, Inc. There will be no financial benefit from the future research on subject data and samples.

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

After subjects have consented to take part in the study, the Sponsor and/or its representatives review their medical records and data collected during the study. Others, including the

following, may review these records and data: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market TBPM-PI-HBr; national or local regulatory authorities and the IRB(s)/IEC(s), which gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects will be assigned a unique identifying number. However, their initials and date of birth may also be collected and used to assist the Sponsor to verify the accuracy of the data, for example, to confirm that laboratory results have been assigned to the correct subject.

The results of studies containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth will be recorded. They may be transferred to, and used in, other countries that may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would be to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

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.

11. REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Period	**Screening**	**Treatment**			**Follow-Up**	
Visit or Study Day	**-1 or 1**	**Days 1 through 14**			**19 ± 2**	**25 ± 2**
Study Day	**Screening [a]**	**1 (Post-Rand.)**	**2 – 14**	**EOT [b]**	**TOC [c]**	**LFU**
Informed Consent	X					
Medical & Surgical History [d]	X					
Height and Weight	X					
Complete Physical Examination [e]	X			X	X	X
Focused Physical Examination [e]		X	X			
Vital Signs (T, P, RR, BP) [f]	X	X	X	X	X	X
Collection of cUTI/ AP signs and symptoms	X	X	X	X	X	X
12-lead ECG [g]	X	X		X	X	
Local labs for eligibility (safety and pregnancy testing) [h]	X					
Local serum creatinine to assess renal function for dose adjustments [h]	X	X	X			
Central labs (blood/urine for safety) [i]	X	X	X	X	X	X
Urine culture [j]	X		X	X	X	X
Blood cultures [k]	X	<----------X---------->				
Rectal swab	X				X	
Study Drug Administration [l]		X	X			
Blood sample for plasma PK [m]			X			
Urine collection for PK [n]		X-------->				
Urinary tract instrumentation status [o]	X		X	X	X	X
Site of care [p]	X	X	X	X	X	X
Investigator assessment of clinical outcome				X	X	X
Prior and concomitant medications	X	X	X	X	X	X
Adverse Events[q]		X	X	X	X	X

AP= Acute Pyelonephritis ; BP = Blood Pressure; cUTI = Complicated Urinary Tract Infection;
ECG = Electrocardiogram; EOT = End-of-Treatment Visit; LFU = Late Follow-up Visit; P = Pulse;
PK = Pharmacokinetic; Rand= Randomization; RR= Respiratory Rate; T = Temperature; TOC = Test-of-Cure Visit

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 hours of randomization) may be used to determine subject eligibility even if performed prior to signing the ICF; however, study-specific assessments, such as triplicate 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 (see Section 7.1.1 for detail). 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 ECGs must be performed in triplicate 1h (±15 min) after the first oral dose administration) (see Section 7.1.2 for detail).
b	IP administration is 7-10 calendar days, or up to a maximum of 14 calendar days for subjects with a baseline blood culture that is positive for uropathogen growth. The EOT Visit occurs on the calendar day or the day following (+1 day) the last dose of study drug. All EOT procedures may be performed the day following last dose of study drug 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 19 ± 2 days. The procedures at the TOC Visit should be performed for all subjects including those who prematurely discontinue study drug.
d	Obtain medical/surgical history, including urological history and any active or inactive conditions diagnosed within the previous 5 years.
e	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 physical examinations between Day 1 and EOT 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.
f	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. 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 subject'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.
g	At Screening, perform 12-lead ECGs in triplicate at 1-5 minute intervals (calculate mean QTcF value for eligibility). On Day 1, perform 12-lead ECGs in triplicate at 1-5 minute intervals 1h (±15 min) after the first oral dose administration. At EOT, perform 12-lead ECGs in triplicate at 1-5 minute intervals 1h (±15 min) after the final oral dose administration. At TOC, perform a single 12-lead ECG.
h	Results from the local blood and urine samples are used to determine eligibility (results can be from samples obtained up to 24 hours 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 LE and WBC in spun or unspun urine). A urine or serum beta human chorionic gonadotropin (β-HCG) pregnancy test (urine or serum 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. Serum creatinine (for CrCl calculation) should be assessed every 3 days for subjects with normal renal function at baseline and at least once daily for subjects 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.
i	The central safety laboratory will perform the following evaluations on blood and urine samples: hematology, coagulation, serum 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 IP), Day 11 (if still receiving IP), Day 13 (if still receiving IP), EOT, TOC, and LFU. In addition, serum β-HCG is performed on all FOCP at the Screening Visit and at the subject's final visit (LFU Visit or time of early withdrawal from the study) by the central laboratory.
j	Obtain urine samples for culture at Screening (urine cultures collected per standard-of-care up to 24 h prior to randomization may be used for eligibility), Day 5, EOT, TOC, and LFU. At LFU, urine culture must be obtained in only subjects with a positive urine culture (growth of urine culture bacterial pathogen(s) $\geq 10^5$ CFU/mL) after the TOC Visit. Urine culture must also be collected on any day a subject is deemed a clinical failure, prior to the start of non-study antibacterial rescue therapy.
k	Collect 2 sets of blood cultures (each set is 1 aerobic and 1 anaerobic blood culture bottle) 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.
l	The TBPM-PI-HBr treatment group will be administered TBPM-PI-HBr 300 mg film-coated tablets orally 600mg q8h (±0.5h) plus a single dummy IV infusion over 30 min q24h (±0.5 h). The ertapenem treatment group will receive ertapenem for IV injection, administered as a 1-gram IV infusion over 30 min q24h (±0.5 h) plus dummy placebo tablets administered orally q8h (±0.5 h).
m	First approximately 70 subjects: Blood samples will be collected on following an oral dose (first, second, or third) on Day 2 at the following time intervals after oral administration of t study drug: 0.25 h (±5 min); 0.5 h (±5 min); 1 h (±15 min), 2 h (±15 min), 8 h (±15 min but prior to the next scheduled dose). For all subjects enrolled after the first 70 subjects, blood samples using sparse sampling (3 samples/subject) will be collected following an oral dose (first, second, or third) on Day 2 at the following time intervals after oral administration of study drug: 1 h (±15 min), 4 h (±1h), and 8 h (±30 min but prior to the next scheduled dose). The exact dose time and the exact PK sample time should be collected for all subjects when collecting PK samples.
n	First approximately 70 subjects, a twenty-four (24) h urine collection will be collected in roughly three (3) 8-h aliquots after the first dose of the study drug on Day 1. These collections should occur as close as possible to the 8 hour time limit. Deviations will only be documented for those collections that occur outside of a 7-9 hour window
o	Record all start times and end times of all urinary tract instrumentation, including but not limited to bladder catheters, stents, nephrostomy tubes, and other urological prosthetic material.
p	Record the site of care (e.g., acute care hospital ward, long-term care facility, outpatient infusion center).
q	AEs will be collected from the time of the first dose of IP.

APPENDIX 2. LIST OF SHORT-ACTING ANTIBIOTICS

Allowed vs. Disallowed Prior Antibiotics

Receipt of any potentially effective systemic antibiotic with activity against Gram-negative uropathogens within the 72-h window prior to randomization is an exclusion criterion. However, subjects may be eligible for the study despite prior antimicrobial therapy if they received a single dose of a short-acting systemic antibiotic within 72 h prior to randomization. For the purposes of this study, a short-acting antibiotic is defined as having a dosage frequency of more than once daily (e.g., q12 h or more frequently). If a subject received a prior short-acting systemic antibiotic that is not listed below, the Investigator must contact the Medical Monitor to ensure subject eligibility.

Antibiotic Class	Allowed Antibiotics (One dose within 72 hours prior to randomization)		Disallowed Antibiotics	
Penicillins	Amoxicillin	Nafcillin	Benzathine/Penicillin-G Procaine	
	Amoxicillin-Clavulanate	Oxacillin		
	Amoxicillin-Sulbactam	Penicillin-G or -V		
	Ampicillin	Piperacillin		
	Ampicillin-Sulbactam	Piperacillin-Tazobactam		
	Dicloxacillin	Ticarcillin-Clavulanate		
Cephalosporins	Cefaclor	Cefpodoxime	Cefixime (400 mg)	
	Cefadroxil	Cefprozil	Ceftriaxone	
	Cefazolin	Ceftaroline		
	Cefdinir	Ceftazidime		
	Cefepime	Ceftibuten		
	Cefixime (200 mg)	Cefuroxime		
	Cefditoren	Cephalexin		
	Cefotaxime	Loracarbef		
Carbapenems	Doripenem	Meropenem	Ertapenem	
	Imipenem			
Fluoroquinolones	Ciprofloxacin		Ciprofloxacin Extended-Release	
			Moxifloxacin	Levofloxacin
Macrolides	Clarithromycin	Erythromycin	Azithromycin	Clarithromycin XL
Tetracyclines	Doxycycline (100 mg)	Minocycline	Doxycycline (200 mg)	Tigecycline
			Minocycline Extended-Release	
Miscellaneous	Clindamycin	Metronidazole		
	Trimethoprim-sulfamethoxazole/ Co-trimoxazole			