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)**
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Spero Therapeutics, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL 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 Subjects with Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)

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Final v1.0	N/A	Initial release	N/A
Final 1.1	7	Added clarification to micro-ITT population definition to include pathogens identified in blood into consideration for micro-ITT assignment	Full rationale is given in section 9
Final 1.1	9	Added rationale for the update in section 7	Necessary as the clarification in Section 7 impacts the definition provided in the Protocol

APPROVAL SIGNATURES

STUDY 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 Subjects with Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)

PROTOCOL NUMBER: SPR994-301

SAP Final version 1.1, 03 September 2020

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LIST OF ABBREVIATIONS

AE	Adverse event
AP	Acute pyelonephritis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
CE	Clinically Evaluable
CFU	Colony-Forming Unit
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
Cr	Serum creatinine
CrCl	Creatinine clearance
CRE	Carbapenem-resistant *Enterobacteriaceae*
CRF	Case report form
cUTI	Complicated urinary tract infections
DSMB	Data Safety Monitoring Board
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End-of-Treatment
ERP	Evaluability Review Plan
ESBL	Extended Spectrum Beta-Lactamase
Hb	Hemoglobin
IPA	Isopropyl Alcohol
ITT	Intention-to-Treat
IV	Intravenous
LFU	Late Follow-Up
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*

NI	Non-inferiority
PD	Pharmacodynamics
PE	Physical Examination
PK	Pharmacokinetics
popPK	Population pharmacokinetics
PT	Preferred term
QTcF	Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SIRS	Systemic inflammatory response syndrome
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment emergent adverse event
TLFs	Tables, listings, and figures
TMP-SMX	Trimethoprim-sulfamethoxazole
TOC	Test-of-Cure
ULN	Upper limit of normal
WBC	White Blood Cells
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analysis and reporting for the study protocol SPR994-301 (version 4.0) dated 26 May 2020. It is based on the final electronic case report forms (eCRFs) dated 01 Apr 2019. This is a Phase 3, randomized, double-blind, double-dummy, multicenter, multinational, prospective study to assess the efficacy, safety and pharmacokinetics (PK) of tebipenem pivoxil hydrobromide (TBPM-PI-HBr, also known as SPR994) administered orally compared to patients receiving ertapenem administered IV for complicated urinary tract infections (cUTI) or acute pyelonephritis (AP).

This SAP does not include the description of the PK and pharmacodynamic (PD) analyses, which are described in a separate stand-alone PK/PD statistical analysis plan.

2. STUDY OBJECTIVES

2.1 Primary Objectives

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

2.2 Secondary Objectives

- To compare clinical cure rates between treatment groups
- To compare microbiological eradication rates between treatment groups
- To assess the population pharmacokinetics (popPK) of TBPM-PI-HBr in patients 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 patients.

2.3 Exploratory Objectives

- To determine whether treatment with TBPM-PI-HBr or ertapenem is associated with enteric colonization with antibiotic-resistant *Enterobacterales*
- To compare microbiological eradication rates and clinical improvement at Day 5 between treatment groups
- To assess clinical, microbiological, and overall responses in patients with cUTI/AP caused by Extended Spectrum Beta-Lactamase (ESBL)-producing *Enterobacterales*.

3. STUDY DESCRIPTION

3.1 Study Design, Planned Interim Analysis, and Review Committees

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 the treatment of cUTI/AP.

This study will enroll approximately 1,200 patients, up to a maximum of 1,450 patients (contingent upon a sufficient number of evaluable patients). Sample size determination details are provided in Section 4; study visits and allowed time windows are specified in Section 8.2.

3.1.1 Randomization

For this study, enrollment occurs at the time of randomization. All patients 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 receive either TBPM-PI-HBr or ertapenem in a 1:1 ratio.

Randomization will be stratified by:

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

Note: Acute pyelonephritis (AP) in this study refers to AP without complicating factors. As per protocol Inclusion Criterion 4, patients who meet the disease definition for cUTI (protocol Inclusion Criterion 4a) and who also have flank pain or costovertebral tenderness are to be randomized as cUTI rather than AP.

3.1.2 PK Data Review Committee

Masked individual and composite PK data from the Sentinel PK Analysis Group (first approximately 35 TBPM-PI-HBr patients enrolled among the first approximately 70 total patients 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 interim plasma PK data; this is not a formal review of either safety or efficacy. Study enrollment will continue uninterrupted during this blinded interim PK data assessment, and the remaining patients 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.

A PK Data Review Committee will verify the protocol-defined TBPM-PI-HBr dose and make recommendations to the sponsor regarding dose adjustment, if applicable. 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 patients into the Microbiological Intent-to-Treat (micro-ITT) Population receiving the amended dose. All details regarding PK Data Review Committee will be provided in the separate charter.

3.1.3 Data Review Committee and Sample Size Reassessment

A blinded sample size reassessment will take place after 70% of the patients have response data at the Test-of-Cure visit (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 patients) to ensure the study has adequate power for the primary outcome measure, up to a maximum of 1,450 patients. In addition, the sample size may be increased based on a lower than expected evaluability rate (the proportion of randomized patients included in the micro-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 for the micro-ITT Population according to pre-specified criteria documented in a sample size reassessment document (DRC charter, v.1.0 dated 13MAR2020). No alpha adjustment will be made as this will be a blinded reassessment, and no treatment group comparison will be performed for any endpoint.

3.1.4 Data Safety Monitoring Committee

The DSMB will review safety data upon enrollment of 25% and 50% of patients.

Responsibilities of the DSMB will be the periodic review of the study data by performing a qualitative and quantitative safety assessment. In addition, the DSMB should determine whether the basic study assumptions remain valid and evaluate whether the overall integrity, scientific merit, and conduct of the study are still acceptable.

Full details regarding the DSMB (e.g., committee composition, timing and scope of review, data analyses, decisions, etc.,) will be specified in the DSMB charter. The DSMB charter will be approved and finalized by the DSMB members and sponsor prior to the first DSMB meeting.

3.2 Study Treatment

Patients will be randomized (enrolled) to one of two treatment arms at a 1:1 ratio, receiving either:

- TBPM-PI-HBr 300 mg film-coated tablet:
    - For patients 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 patients 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: 1 gram IV q24h (±0.5 h) for all patients (CrCl >30 mL/min)
    - Plus 2 dummy oral tablets q8h (±0.5 h) for patients with normal renal function or mild renal insufficiency (CrCl >50 mL/min)
    - Plus 1 dummy oral tablet q8h (±0.5 h) for patients with moderate renal insufficiency

(CrCl >30 to ≤50 mL/min)

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

4. SAMPLE SIZE AND POWER CALCULATION

Original assumptions

Assuming a response rate of 70% for both treatment groups, a pre-specified non-inferiority (NI) margin of 10%, a 1:1 randomization ratio, and a one-sided significance level of 0.025, a trial including 884 evaluable patients in the micro-ITT Population would have approximately 90% power to show NI within a 10% margin. This trial aims to recruit 884 evaluable patients into the micro-ITT Population. Assuming 75% of randomized patients met the criteria for inclusion in the micro-ITT Population, approximately 1,180 patients will be recruited to ensure 884 evaluable patients into the micro-ITT Population. This size study would also have 90% power for an analysis of the microbiologically evaluable (ME) Population, assuming a 75% response rate and 67% of randomized patients are included in the ME Population. A blinded assessment of overall evaluability rates (the proportion of randomized patients 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 1,450 patients according to pre-specified criteria.

Changes Due to the COVID-19 Pandemic

At the time of the blinded assessment of response rate and evaluability rate (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 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 response 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 on 05-May-2020 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 US FDA (as detailed in Section 8.8.1). 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.

5. ANALYSIS ENDPOINTS

5.1 Primary Endpoints

Efficacy: Overall response (combined clinical cure plus microbiological eradication) at TOC in the micro-ITT Population. See Sections 6.1, 8.2, and 8.8 for further details.

Safety: Assessment of safety and tolerability up to the Late Follow-Up visit (LFU) in the Safety Population. See Sections 8.2 and 8.9 for more details.

5.2 Secondary Endpoints

- Overall response (combined clinical cure plus microbiological eradication) at TOC in the ME Population.
- Clinical cure at EOT, TOC, and LFU Visits in the micro-ITT, clinically evaluable (CE), and ME Populations.
- Per patient and by-pathogen microbiological eradication at EOT, TOC, and LFU in the micro-ITT and ME Populations.
- Sensitivity analyses of the primary efficacy endpoint (overall response at TOC in the micro-ITT Population) in key subgroups, including:
    - Stratified infection category
    - Stratified age category
    - Country/Region.

  Endpoints for analyses in additional subgroups of interest are described in Section 8.8.5
- Time (days) to resolution or improvement of signs and symptoms of cUTI and AP present at baseline in the micro-ITT Population.
- Time (days) to defervescence in micro-ITT patients with a documented fever at Screening or Day 1.
- Rate of clinical relapse at the LFU Visit in the micro-ITT Population.
- Rates of colonization, superinfection and new infection in the micro-ITT Population.
- Determine PK parameters (e.g., Vd, Cmax, AUC, T>MIC) in TBPM-PI-HBr recipients in the PK Population in the first 70 patients enrolled (Sentinel PK Group).

  Detailed descriptions of PK and PD analyses are provided in a separate PK/PD SAP and will be separately reported.

5.3 Exploratory Endpoints

- Enteric colonization with antibiotic (carbapenem)-resistant *Enterobacterales* at the TOC in the micro-ITT Population.
- Per-patient microbiological eradication and per-patient clinical improvement at Day 5 in the micro-ITT Population.
- Per-patient and by-pathogen microbiological response at TOC, overall and clinical response at TOC by-baseline pathogen and resistance mechanism among patients with cUTI/AP caused by ESBL-producing *Enterobacterales* in the micro-ITT and ME Populations.

5.4 Additional Efficacy Endpoints

- Overall response at EOT will be summarized in the micro-ITT and ME Populations.
- Clinical cure at EOT and TOC by baseline pathogen in the micro-ITT and ME Populations.
- Response in patients infected with cUTI/AP due to resistant Gram-negative pathogens for the overall response, and per-patient and by-pathogen clinical and microbiological responses at EOT and TOC in the micro-ITT and ME Populations.

6. RESPONSE DEFINITIONS

6.1 Overall Response

The overall response for the primary and secondary endpoints outlined above is defined as the combination of clinical (Section 6.2) and microbiological (Section 6.3) response at the respective visit.

For the overall (combined) response at EOT and TOC, patients will be categorized as:

- Responder: clinical cure plus favorable microbiological response
- Non-responder: clinical failure only, unfavorable microbiological response only, or both
- Indeterminate response: indeterminate clinical response plus favorable microbiological response, indeterminate microbiological response plus favorable clinical response, or indeterminate clinical and microbiological response

Table 1: Summary of overall (combined) response outcomes at EOT and TOC

Clinical Outcome	Per-patient Microbiological Response		
	Favorable	Unfavorable	Indeterminate
Cure	Responder	Non-responder	Indeterminate
Failure	Non-responder	Non-responder	Non-responder
Indeterminate	Indeterminate	Non-responder	Indeterminate

6.2 Clinical Response

Clinical response at EOT, TOC, and LFU are defined based on assessment by the Investigator of change in baseline signs and symptoms of cUTI/AP. Clinical response at Day 5 are programmatically derived based on the case report form (CRF) data.

Clinical response at Day 5:

- Clinical improvement: Patient is alive with resolution or improvement by at least one grade in at least 1 baseline sign/symptom AND no worsening of any baseline signs/symptoms AND development of no new signs/symptoms of cUTI/AP requiring the initiation of a non-study antibacterial therapy for the index infection (defined as no concomitant antibacterial medication for primary study condition prior to Day 5)
- No clinical improvement: Lack of resolution or improvement by at least one grade in at least 1 baseline sign/symptom of cUTI/AP OR development of new signs/symptoms of cUTI/AP requiring the initiation of a non-study antibacterial drug therapy, OR death
- Indeterminate clinical response: Insufficient data are available to determine a clinical response at Day 5

Clinical response at EOT, TOC:

- Clinical cure: Patient is alive with complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted
- Clinical failure:
    - Persistence or worsening of baseline signs/symptoms of cUTI or AP and/or development of new symptoms requiring the initiation of a non-study antibacterial drug therapy
    - Death
    - TOC only: Patient previously met criteria for failure at EOT
    - Continuation of study therapy beyond the protocol-specified 10 days of treatment (or more than 14 days of treatment for bacteremic patients)
- Clinical indeterminate: Insufficient data are available to determine if the subject is a cure or failure (e.g., patient is lost to follow-up or has missing data at the respective visit)

Clinical response at LFU are defined as follows:

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

  Clarification: Includes patients who remained free of new or recurrent signs and symptoms up to and including the LFU visit, such that no further antimicrobial therapy for the treatment of cUTI/AP was warranted.

- Clinical relapse: Met criteria for clinical cure at TOC, but new signs and symptoms of cUTI or AP are present at the LFU and the patient requires antibiotic therapy for the cUTI

  Clarification: Includes patients who developed new or recurrent signs and symptoms

anytime from TOC and up to and including the LFU requiring additional antibiotic therapy for the treatment of cUTI/AP

- Clinical indeterminate: Insufficient data are available to determine if the patient is a sustained clinical cure or clinical relapse
- Clinical failure: Patient previously met criteria for failure at EOT or TOC

6.3 Microbiological Response

Microbiological response will be derived by-pathogen and per-patient based on individual response for each baseline uropathogen isolated from a urine or blood source. A favorable by-pathogen microbiological response (eradication or presumed eradication) will be derived from the individual response for each baseline uropathogen. A favorable per-patient microbiological response requires a favorable response for all baseline pathogens.

By-pathogen microbiological response

The by-pathogen microbiological response at Day 5, EOT and TOC are defined as outlined in Table 2 below. Microbiological response at Day 5 are presented by-patient only using the assessment of isolates based on Table 2.

Table 2: Microbiological response categories at Day 5, EOT, and TOC for each pathogen identified at baseline

Response	Pathogen found in urine only at BL	Pathogen found in blood only at BL [1]	Pathogen found in urine and blood at BL [1]
Microbiological eradication	• Baseline pathogen is reduced to $<10^3$ CFU/mL on urine culture	• Absence of baseline pathogen on post-baseline blood culture and • Same baseline pathogen is $<10^3$ CFU/mL on urine culture or not present	• Absence of baseline pathogen on most-recent post-baseline blood culture and • Baseline pathogen is $<10^3$ CFU/mL on urine culture or not present
Presumed microbiological eradication (specific to blood pathogens)	N/A	• Clinical response of cure (or clinical improvement response) when missing post-baseline blood culture and • Baseline pathogen is $<10^3$ CFU/mL on urine culture or not present	N/A
Microbiological persistence [2]	• Isolation from urine culture of $\geq 10^3$ CFU/mL	• Isolation from urine culture of $\geq 10^3$ CFU/mL Or • Presence of baseline pathogen in most-recent post-baseline blood culture	• Isolation from urine culture of $\geq 10^3$ CFU/mL Or • Presence of baseline pathogen in most-recent post-baseline blood culture
Presumed microbiological persistence	NA	• Patient response is clinical failure or no clinical improvement) and no post-baseline blood culture is available	

Response	Pathogen found in urine only at BL	Pathogen found in blood only at BL [1]	Pathogen found in urine and blood at BL [1]
Microbiological persistence with increasing MIC [3]	Pathogen response is "persistence" at EOT or TOC and post-baseline urine and/or blood isolate displays ≥4 fold higher MIC to study therapy received [4]		
Microbiological indeterminate	No follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason (e.g., or the follow-up urine culture is considered contaminated)	Patient discontinued prior to visit and no cultures are available.	No follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason (e.g., or the follow-up urine culture is considered contaminated)

BL = Baseline; MIC = Minimum Inhibitory Concentration; EOT = End-of-Treatment; N/A = Not Applicable; TOC = Test-of-Cure, CFU = colony-forming unit

[1] Post-baseline blood cultures are to be taken only if positive at baseline or as clinically indicated. Post-baseline blood cultures should be repeated until negative. In the absence of a post-baseline blood culture when one is expected, the baseline blood-pathogen response will be derived or presumed from the clinical response (i.e., presumed eradication or presumed persistence). All cases involving positive post-baseline blood cultures will be manually reviewed.

[2] Pathogens with a microbiological persistence response at EOT will be considered a persistence response at TOC

[3] Derived for EOT and TOC only

[4] Tebipenem and ertapenem MICs have dilutions up to 8 µg/mL; therefore, MIC reported as '>8' will be considered as 16 µg/mL when microbiological persistence with increasing MIC is derived. For baseline pathogens with MIC to study drug at baseline =8 or '>8' microbiological persistence with increasing MIC won't be derived.

The by-pathogen microbiological response at LFU is defined as follows:

- Sustained microbiological eradication: Microbiological eradication of baseline uropathogen at TOC and no subsequent urine culture at any time after TOC demonstrating recurrence of the original baseline uropathogen at $\geq 10^5$ CFU/mL
- Microbiological recurrence: Microbiological eradication of baseline uropathogen at TOC and subsequent urine culture demonstrates recurrence of baseline uropathogen at $\geq 10^5$ CFU/mL or in blood culture at any time up to and including the LFU
- Microbiological indeterminate: The follow-up urine culture (if available) cannot be interpreted for any reason (e.g., culture is considered contaminated), or other circumstances preclude classification as eradication or recurrence
- Pathogens with a microbiological persistence (or presumed persistence) response at EOT or TOC will be considered as persistence at LFU

When it is not possible to programmatically assign by-pathogen microbiological response using the algorithms described above, by-pathogen microbiological response will be assigned based on sponsor blinded review of the data.

Per-patient microbiological response:

Per-patient microbiological response at each visit will be categorized as favorable, unfavorable or indeterminate as outlined in Tables 3 and 4 and are programmatically derived based on

microbiological response noted above for all baseline uropathogens isolated from urine and/or blood.

A favorable per-patient microbiological response requires a favorable response for all baseline pathogens (eradication or presumed eradication for Day 5, EOT and TOC; sustained microbiological eradication for LFU) isolated from urine and/or blood. If at least one baseline pathogen has microbiological response of persistence (for Day 5, EOT, or TOC) or recurrence for LFU, a per-patient microbiological response will be assigned as unfavorable.

Per-patient microbiological responses at Day 5, EOT and TOC are defined as outlined in Table 3. Per-patient microbiological response at LFU is defined as outline in Table 4.

Table 3: Per-patient microbiological response outcomes at Day 5, EOT, and TOC

Category	Criteria
Favorable	All baseline uropathogen(s) have a response of eradication or presumed eradiation at the specified visit (Day 5, EOT or TOC)
Unfavorable	• The response of at least 1 baseline pathogen is persistence or presumed persistence. • Subjects with an unfavorable microbiological response at EOT will be considered unfavorable at TOC
Indeterminate	The response of at least 1 baseline pathogen is indeterminate and there is no response of persistence or presumed persistence for any baseline pathogen

EOT = End of Treatment, TOC = Test-of-Cure.

Table 4: Per-patient microbiological response outcomes at LFU

Category	Criteria
Favorable	The response of all baseline pathogens must be sustained microbiologic eradication
Unfavorable	• The response of at least 1 baseline pathogen is microbiologic recurrence • Subjects with an unfavorable microbiological response at TOC will be considered unfavorable response at LFU
Indeterminate	The response of at least 1 baseline pathogen is indeterminate and there is no outcome of recurrence or persistence for any baseline pathogen

TOC = Test-of-Cure, LFU = Late Follow-up.

Additional microbiological response for post-baseline pathogens include the following:

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

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

6.4 Exploratory response definitions

Enteric colonization will be defined as new post-baseline detection of carbapenem-resistant *Enterobacterales* from a post-baseline rectal swab in patients who were negative at baseline.

CRE Colonization at TOC will be defined as per algorithm described in Table 5.

Table 5: CRE Colonization at TOC

CRE Colonization at TOC	Screening Visit	TOC Visit	Explanation
NO	Rectal swab culture identified as **Meropenem-resistant *Enterobacterales*** (Meropenem MIC ≥ 4 µg/mL) at screening visit **[CRE positive at screening visit]**	Rectal swab with either the **same genus and species** of meropenem-resistant *Enterobacterales* identified at screening visit **or** negative rectal swab culture	CRE was already present at baseline screening and no indication either study drug promoted CRE colonization
YES	**Either** no *Enterobacterales* (no organism) **or** meropenem-susceptible *Enterobacterales* (meropenem MIC ≤ 1 µg/mL) identified at screening visit [CRE negative at screening visit]	Rectal swab that yields a **meropenem-resistant *Enterobacterales*** (meropenem MIC ≥ 4 µg/ml) at TOC visit **[CRE positive at TOC visit]**	New CRE at TOC that was not present at screening

CRE = carbapenem-resistant *Enterobacterales*, MIC = Minimum inhibitory concentration, TOC = Test-of-Cure.

7. ANALYSIS POPULATIONS

The analysis populations for the study are defined as follows:

- **Intent-to-Treat (ITT) Population**: All patients who were randomized, regardless of whether they received any study drug. Patients will be summarized by the treatment to which they were randomized.
- **Safety Analysis Population**: Randomized patients who received any amount of study drug. Patients will be summarized by the treatment which they received.
- **Microbiological Intent-to-Treat (micro-ITT) Population**: All randomized patients 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 and/or positive Screening blood culture with isolation of one or more uropathogens. Patients with Screening urine culture growth of more than 2 species of uropathogens will be excluded from the micro-ITT Population, regardless of colony count unless a uropathogen was also isolated from blood. Any patient with cUTI or AP caused by a pathogen that is typically not expected to respond to study drug e.g., *Acinetobacter* spp., *Stenotrophomonas* spp., *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus*

aureus (MRSA) as outlined in the SPR994 Evaluability Review Plan (ERP, v.3 dated 20 Aug 2020) will be excluded from this analysis population. In addition to non-fermenting Gram-negative bacilli and MRSA, baseline uropathogens that are non-susceptible to meropenem will be excluded from the micro-ITT Population.

- **Clinically Evaluable (CE) Population** (defined in detail in SPR994-301 ERP v.3 dated 20 Aug 2020): The CE Population will be defined for each visit (CE-EOT, CE-TOC, and CE-LFU) for the analyses in the CE Population at each respective visit and is a subset of the ITT Population and includes patients who have no important protocol deviations that would affect the assessment of efficacy and had an response assessed as clinical cure or clinical failure at EOT, TOC, and/or LFU. Specific criteria for exclusion from the CE Population are specified in the ERP v.3 dated 20 Aug 2020.
- **Microbiologically Evaluable (ME) Population:** The ME Population includes patients who meet the definitions of both the micro-ITT Population and CE Population and will be defined for each visit (ME-EOT, ME-TOC, and ME-LFU) for the analyses in the ME Population at each respective visit as outlined in the ERP v.3 dated 20 Aug 2020.
- **PK Population:** All patients 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 patients. The Sentinel PK Analysis Group includes the first approximately 35 TBPM-PI-HBr-treated patients among the first approximately 70 patients enrolled, and the Sparse PK Analysis Group includes all patients enrolled thereafter. PK data for both groups in the PK Population will be used for all PK analyses as described in the separate PK SAP.

8. ANALYTICAL PLAN AND STATISTICAL METHODS

8.1 General Conventions and Statistical Considerations

All analyses will be performed using SAS® statistical analysis software (SAS, SAS/GRAPH and SAS/STAT; version 9.4 or higher of SAS for Windows [SAS Institute Inc.; Cary, NC, USA]).

Descriptive statistics for continuous variables (if not stated otherwise) will include the number of patients, mean and standard deviation, median, and minimum and maximum values. All raw data will be presented to the original number of decimal places. Means, medians, and confidence intervals will be presented to 1 more decimal place than in the raw data. Standard deviations will be presented to 2 more decimal places than in the raw data. Summary statistics for categorical variables will contain count and percentage. Percentages will be presented to one decimal, except for one hundred percent, which will be presented as 100%. Unless otherwise specified, percentages for baseline summaries will be based on the total number of patients in the treatment arm or overall for the indicated population (dependent on table column heading); percentages for post-baseline summaries will be based on the total number of patients with non-missing values in the treatment arm or overall.

Data will be listed individually by patient.

Tables for the ITT, micro-ITT, ME, and CE Populations will be produced using randomized treatment groups. Tables for the Safety Population will be produced using actual treatment received by a patient.

8.2 Definition of Baseline, Study Visits, and Visit Windows

Generally, baseline is defined as the most recent value prior to the start of treatment with study drug, within 48 hours prior to the first dose of study medication with the exception of:

- Baseline pathogen may originate from any culture taken within 48 hours prior to first dose or on study day 1.
- ECG will be performed in triplicate. Average of the triplicate is used in the analysis. Baseline ECG value is defined as average of three latest assessments prior to first dose.
- Maximum daily temperature will be presented in the tables. According to the protocol, if screening and study Day 1 visit occurred on same calendar day, only one record will be marked as maximum daily temperature. For these cases, the baseline value will be defined as maximum temperature from pre-dose assessments and value for study Day 1 will be equal to maximum post-dose temperature from this calendar day.

Safety and efficacy data will be analyzed according to the visits recorded in the eCRF. Out-of-window visits will affect evaluability in CE populations as detailed in the SPR994-301 ERP (v.3 dated 20Aug2020). Protocol-defined timing of visits and windows are outlined as follows:

- EOT: Occurs on the calendar day or the day following (+1 day) the last dose of study drug
- TOC: Day 19 ± 2 days
- LFU: Day 25 ± 2 days.

8.3 Microbiological data definitions

The process of determination of uropathogen from screening urine and blood cultures is specified in the SPR994-301 ERP (v.3 dated 20 Aug 2020).

By-pathogen microbiological responses for baseline pathogens will be derived programmatically (as specified in Section 6.3) based on the final output provided by Spero from the blinded microbiological and clinical evaluability review and clinical response from the clinical database.

The final output will be in the form of a SAS dataset where pathogens for each patient at each visit will be identified after adjudication. The dataset will also mark patients who are to be excluded from the micro-ITT Population due to carbapenem-resistant pathogens.

8.4 Handling of Missing Data

Imputation methods will be used for missing dates as listed below. Original, non-imputed dates will be provided in all listings.

No other methods will be utilized for handling missing data.

8.4.1 Adverse Events

For adverse events (AEs), imputation rules will be used to have any AEs with missing dates be classified as treatment-emergent if there is any possibility for that to be the case. Therefore, the following will be used for imputation of incomplete AE dates.

For start date,

- If only the day component is missing and the year and month of the AE start are not the same as the year and month of the treatment start, then the AE start date will be imputed as the first day of the month. If the year and month of the AE start match the year and month of the treatment start, then the treatment start date will be used to impute the start date of the AE.
- If both day and month components are missing and the year does not equal the year of treatment start, then use January 01. If the year matches the year of treatment start, then use the treatment start date as to impute the start date of the AE.

For end date,

- If only the day component is missing, then use the last day of the month.
- If both day and month components are missing, then use December 31.
- Stop dates will not be imputed if AE is listed as ongoing.

If both start and end dates are completely missing, they will not be imputed, and AEs will be considered treatment-emergent.

8.4.2 Prior and Concomitant Medication

In order to simplify the process of differentiation between the prior and concomitant medications (defined in Section 8.7.2), the following will be used for imputation of incomplete medication dates:

For start date,

- If only the day component is missing, then use the first day of the month;
- If both day and month components are missing, then use January 01.

For end date,

- If only the day component is missing, then use the last day of the month.
- If both day and month components are missing, then use December 31.

Stop dates will not be imputed if medication is ongoing at LFU or discharge from the study.

If both start and end dates are completely missing, they will not be imputed, and medication will be considered both prior and concomitant.

8.5 Patient Disposition

The number and percentage of patients randomized will be presented. The summaries will be generated by country and region and by center.

The number and percentage of patients in each analysis population together with reasons for exclusion from each population will be provided.

Patients receiving treatment, completed the treatment period, discontinued prematurely from the study treatment along with the reason for discontinuation, completed the post-treatment period, and discontinued from the post-treatment along with the reason for discontinuation will be summarized by number and percentage for all patients in the Safety, ITT, and micro-ITT Populations, by treatment and overall. Summaries will include COVID-19 as a separate reason for treatment/study discontinuation.

Listings will be provided for study disposition, including reasons for exclusion and discontinuation from the study.

8.6 Protocol Deviations

Protocol deviations will be tabulated in ITT Population. The summary will include number and percentage of patients with at least one major deviation, at least one minor deviation and at least one major deviation of each category. A similar summary of protocol deviations will be produced for those deviations related to COVID-19 and will be summarized for the ITT Population.

A listing of all protocol deviations, along with their categorization as major or minor, will be provided for all patients in the ITT Population. Protocol deviations related to COVID-19 will be flagged in this listing.

8.7 Patient Characteristics

All tables in this section will be run for the Safety and micro-ITT Populations.

Baseline demographics will be summarized by treatment group and overall to include age and age category at time of informed consent in years as recorded on CRF (≥18 to <65 years, ≥65 to <75, ≥75 years), sex, race (American Indian or Alaska Native /Asian/Black or African American/Native Hawaiian or Other Pacific Islander/White/Other/Not Reported; note that the categories of Other/Not Reported/American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander race categories will be grouped into Other for subgroup analysis), ethnicity (Hispanic or Latino/Not Hispanic or Latino/ Not Reported), region (Central and Eastern Europe, South Africa, United States), BMI at screening (kg/cm^2).

Baseline clinical characteristics will be summarized by treatment group and overall to include baseline diagnosis [AP vs. cUTI]; estimated creatinine clearance [CrCl], central lab values or if missing, EDC calculated local lab values) as calculated by Cockcroft Gault method (Cockcroft and Gault 1976) (≤30, >30 to ≤50, >50 mL/min), bacteremia at baseline (Y/N), receipt of prior systemic antibiotics (Y/N), modified systemic inflammatory response syndrome (SIRS) criteria, infection due to resistant Gram-negative uropathogen (ESBL-phenotype, FQ-NS, TMP/SX-R); per criteria outlined in Table 6 (Section 8.7.3).

The summary of baseline diagnosis will also include subsets of cUTI split by cUTI with and without AP, as detected by the presence or absence of any severity of costovertebral angle tenderness or flank pain at baseline. Specifically, a patient with cUTI who has costovertebral angle tenderness or flank pain at baseline (any severity) reported on CRF at baseline is considered to have cUTI with AP, while a patient with cUTI who does not have costovertebral angle tenderness or flank pain at baseline reported on CRF at baseline is considered to have cUTI without AP (i.e., complicated cystitis).

Modified SIRS criteria at baseline will be derived programmatically. A patient is considered to have SIRS at baseline if two or more of the following symptoms are present at baseline:

- Body temperature <36° C or >38° C
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute
- White blood cell count <4 x 10^9 cells/L or >12 x 10^9 cells/L

Listings will be provided for all demographic and baseline variables for the ITT Population.

8.7.1 Medical and Surgical History and Current Medical Conditions

Urinary tract signs and symptoms (term and severity) will be summarized for each visit by treatment arm and overall for all patients in the Safety and micro-ITT Populations.

Medical and surgical history (both prior and concurrent conditions and procedures) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 21.0 or later). For each System Organ Class (SOC) and preferred term (PT), summaries will be presented by number and percentage of subjects having at least one occurrence of a disease. Summaries will be presented by treatment and overall, for all subjects in the Safety and ITT Populations.

Listings will be provided for all patients' medical history and current medical conditions and procedures for the ITT Population.

8.7.2 Prior and Concomitant Medication

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD; WHODRUG/2006QA or newer version). A medication is considered

prior if administered within 30 days (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) of the date of first dose of study drug. A concomitant medication is defined as any medication taken during the period from the date of first dose of study drug through the late follow-up visit. A medication that was started before the date of first dose and continues after the first dose will be included as both a prior and concomitant medication.

Prior antibiotics and concomitant (both antibiotic and non-antibiotic) medications will be summarized by the Anatomical Therapeutic Chemical (ATC) class (ATC 2 and ATC 4) and PT. Antibiotic and non-antibiotic treatments will be summarized separately. The summary for concomitant antibiotics treatment will be further split to: any concomitant antibiotic, concomitant antibiotics for cUTI/AP, and concomitant antibiotics given for other infections. Summaries will be presented by treatment and overall, for all patients in the Safety and micro-ITT Populations.

Listings of all prior and concomitant medications (antibiotic and non-antibiotic separately), prior and concomitant non-drug therapies will be provided for all patients in the ITT Population.

8.7.3 Baseline pathogens

All summaries specified in this section will be done separately for baseline pathogens isolated from urine and/or blood and for baseline pathogens isolated from blood (if not noted otherwise in the section text). All summaries will be presented in micro-ITT and ME-TOC populations.

Qualifying blood and/or uropathogens isolated at $\geq 10^5$ CFU/mL from baseline urine cultures will be summarized by treatment group and overall for patients in the micro-ITT and ME-TOC Populations. Baseline pathogen summaries will be presented by genus and species within each group of pathogens for uropathogens isolated from urine and/or blood and separately for uropathogens isolated from blood.

The number of patients with *Enterobacterales* pathogens will be presented in- micro-ITT and ME Populations.

All pathogens isolated from urine and/or blood cultures will undergo identification and susceptibility testing at both the local and central laboratory. Identification and susceptibility results from the central laboratory will be used by default for evaluability and response assessments where available as described in the ERP (v3, dated 20 Aug 2020). However, where central laboratory data are not available, local laboratory data may be utilized as defined in the ERP (v3, dated 20 Aug 2020).

In vitro testing results of baseline pathogen susceptibility to tebipenem, ertapenem, ceftazidime, levofloxacin and trimethoprim/sulfamethoxazole will be separately summarized for all pathogens by treatment group and overall for the micro-ITT and ME-TOC Populations. For ertapenem, levofloxacin and trimethoprim/sulfamethoxazole results will be presented as "susceptible" and "nonsusceptible" (including subsets of 'intermediate' or "resistant" or "unknown"); for TBPM-PI-HBr, results will be presented by tebipenem MIC category as ≤ 0.25 mg/L, >0.25 mg/L and 'missing'.

Target antibiotic-resistant phenotypes of interest for baseline *Enterobacterale*s isolates will be identified based on the susceptibility criteria outlined in Table 6.

Table 6. Resistant pathogen phenotypes for *Enterobacterales* isolates

Phenotype	Criteria	Comment
ESBL-phenotype	Ceftazidime MIC ≥2 µg/mL (or ceftriaxone MIC ≥2 µg/mL if ceftazidime susceptibility is not available)	Criteria for selecting isolates for molecular characterization of β-lactamase genes
Fluoroquinolone-nonsusceptible	Levofloxacin MIC ≥1 µg/mL	CLSI breakpoint for intermediate and resistant susceptibility
Trimethoprim-sulfamethoxazole-resistant	TMP-SMX MIC ≥4 µg/mL	CLSI breakpoint for resistance

ESBL = Extended Spectrum Beta-Lactamase; MIC=Minimum Inhibitory Concentration; CLSI = Clinical and Laboratory Standards Institute; TMP-SMX = Trimethoprim-sulfamethoxazole

If more than one pathogen of the same species is isolated in a patient, the pathogen with the highest Minimum Inhibitory Concentration (MIC) value for that phenotypic criteria will be selected.

Baseline pathogen susceptibility phenotypes will be summarized on a by-pathogen and per-patient basis as outlined below (these summaries will only be done based on pathogens isolated from urine and/or blood):

- **By-pathogen** summary tables will present the total number of pathogens of each phenotype presented by genus and species. ESBL, FQ and TMP/SMX categories are not mutually exclusive (e.g., a pathogen that is ESBL-phenotype but FQ-susceptible should still be counted in both summary rows). However, a patient with 2 *E. coli* isolates, one FQ-NS and one FQ-S would be counted only once in the summary rows for FQ phenotype by the highest levofloxacin MIC.
- **Per-patient** summary tables will present the total number patients with any resistant pathogen in each phenotype category based on isolate with highest MIC for the phenotype category; e.g., if at least one pathogen isolated in a patient is considered ESBL-phenotype, a patient will be considered ESBL-phenotype).

The distribution of baseline pathogen MIC to study drugs and/or those outlined for resistance selection (Table 6) will be presented by treatment group and overall for each pathogen/pathogen category for the micro-ITT and ME-TOC Populations. The following summaries will be performed:

- Distribution of tebipenem, ertapenem, ceftazidime, levofloxacin, and trimethoprim-sulfamethoxazole MIC of baseline *Enterobacterales* pathogens

- Distribution of tebipenem and ertapenem MICs of *Enterobacterales* pathogens by resistance-pathogen phenotype:
    - ESBL-phenotype vs. non-ESBL-phenotype
    - Fluoroquinolone-nonsusceptible vs. Fluoroquinolone-susceptible
    - Trimethoprim-sulfamethoxazole (TMP-SMX)-resistant vs. TMP-SMX-susceptible

In addition, MIC distribution summaries will include susceptibility categories (where applicable), MIC frequencies and summary statistics including minimum and maximum values as well as MIC_{50} and MIC_{90} values and range. Pathogens will be grouped to *Enterobacterales* and Non-fermenting Gram-negative Bacilli in the summary table.

MIC values will be derived programmatically: MIC values will be ordered from lowest to highest with a greater than sign taking a higher value (e.g., 8 is first then >8 is next). Cumulative percentage will be determined from lowest to highest value. MIC_{50} will be selected as the first value equal to or greater than 50%. MIC_{90} will be derived in a similar way. The MIC_{50} will only be calculated when ≥5 isolates are available, whilst the MIC_{90} will only be calculated when ≥10 isolates are available.

Culture results and susceptibility testing results for each baseline pathogen will be listed by patient and treatment group for the ITT Population (patients included into the micro-ITT Population will be flagged).

8.8 Efficacy Analysis

8.8.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is overall response (combined clinical cure and microbiological eradication) at TOC in the micro-ITT Population. Patients with an indeterminate outcome at TOC for either the clinical or microbiological response at TOC will be defined as indeterminate for the primary analysis (Table 1) and will be included in the denominator for the calculation of overall response rate and confidence intervals.

The number and percentage of patients in each treatment group in each response category (success, failure, or indeterminate) at TOC will be reported.

The null and alternative hypotheses 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 Miettinen and Nurminen (Stratified Miettinen and Nurminen CIs with Cochran-Mantel-Haenszel weights will be used. Stratification variables will be baseline diagnosis (AP vs. cUTI) and age at informed consent (≥18 to <65 years vs. ≥65 years)). If the lower limit of the 95% CI for the difference between treatment groups in overall response (responder) is greater than -12.5%, non-inferiority will be declared.

Reasons for non-responders and indeterminate at TOC will be summarized in the micro-ITT using number and percentages.

8.8.2 Analysis of Secondary Efficacy Endpoints

To avoid repetition in the Analysis of Additional Efficacy Endpoints section below (Section 8.8.4), and since the additional efficacy endpoints listed below are to be analyzed in the same manner as some secondary efficacy endpoints, the following additional efficacy endpoints are included in this section:

- Overall response at EOT in the micro-ITT and ME Populations.
- Clinical cure at EOT and TOC by baseline pathogen in the micro-ITT and ME Populations

Overall response at EOT in the micro-ITT Population and the overall response at EOT and TOC in the ME Population will be defined similarly to the primary endpoint and summarized using number and percentages. Risk difference between the two treatment arms will be calculated along with 95% CIs in the same way as for the primary endpoint.

If a patient is assessed as a clinical failure at EOT or TOC, the patient is automatically considered a failure at subsequent visits, and will be programmatically derived as a clinical failure where clinical response is missing due to missed visit. Otherwise clinical response will be programmatically derived as indeterminate if clinical response is missing due to missed visit. Patients with missing visits will be excluded from corresponding CE population due to clinical indeterminate (due to missed visits) regardless of programmatically assigned clinical failure response.

Analyses in the ME and CE populations will be performed using the ME and CE populations derived for each respective visit (e.g., ME-EOT, ME-TOC, ME-LFU).

Clinical response at EOT, TOC, and LFU will be summarized by number and percentages in the micro-ITT, CE, and ME Populations. The risk difference and 95% CIs will be calculated as for the primary endpoint. Reasons for clinical failure response will be presented by visit in the micro-ITT Population.

Clinical response by pathogen for the EOT and TOC will also be summarized in the micro-ITT and ME Populations.

Per-patient microbiological response at EOT, TOC, and LFU will be summarized by number and percentages in the micro-ITT and ME Populations. The risk difference and 95% CIs will be calculated as for the primary endpoint.

By-pathogen microbiological response at EOT, TOC, and LFU will be summarized by counts and percentages in the micro-ITT and ME Populations.

All by-pathogen summaries will be presented separately for isolates from urine and/or blood and for isolates from blood.

Time (days) to resolution or improvement of signs and symptoms of cUTI and AP present at baseline will be defined as follows: date of first visit at which all baseline sign/symptoms have improved by at least one grade with worsening of none or development of no new signs/symptoms of the index infection– date of randomization. If the resolution/improvement did not occur, then the data is censored at the date of the last non-missing symptom assessment. The analysis will be performed in the micro-ITT Population.

Time (days) to defervescence in micro-ITT patients with a documented fever at Screening or Day 1 will be defined as follows: date of first post-baseline temperature measure with maximum daily temperature ≤38° C – randomization date. If the temperature does not ever fall below the threshold, the patient will be considered censored at the date of the last temperature assessment. Patients without fever (defined as temperature ≤38.0° C) at baseline will be excluded from this analysis.

Time to resolution or improvement of signs and symptoms and time to first defervescence will be summarized using a Kaplan-Meier plot including the significance level from the log rank test, and also as the mean, median, minimum, and maximum number of days and number of patients.

Rates of superinfection, colonization, and new infection at respective visits will be summarized in the micro-ITT Population.

Subgroup analysis is described in Section 8.8.5.

8.8.3 Analysis of Exploratory Efficacy Endpoints

Rate of enteric colonization with antibiotic (carbapenem)-resistant *Enterobacterales* at TOC will be summarized by treatment arm and overall in the micro-ITT Population and will be summarized by pathogen, if available.

Per-patient microbiological response and per-patient clinical improvement at Day 5 will be summarized for the micro-ITT Population.

Reasons for clinical non-response and indeterminate (such as death, new signs and symptoms requiring antibiotic therapy, lack of improvement, signs and symptoms are not assessed) at the Day 5 will be summarized in the micro-ITT Population.

Per-patient clinical response, microbiological response, and overall responses at TOC among patients with cUTI/AP caused by resistant pathogen phenotypes (Table 6, phenotype categorization for a patient will be determined based on baseline pathogens isolated from urine and/or blood) will be summarized in the same manner as for the primary endpoint in micro-ITT and ME Populations, and the 95% CI will be produced using the same method as for the primary analysis. If there are insufficient patients in each strata in order to perform the stratified analysis, the (unstratified) method of Miettinen and Nurminen will be used.

For a subset of Gram-negative pathogens meeting phenotypic (MIC) screening criteria for the presence of a β-lactamase, molecular characterization of β-lactam resistance mechanisms will be evaluated in vitro, allowing for the analyses of response by resistance mechanism among patients with cUTI/AP caused by caused ESBL-producing *Enterobacterales*. The per-patient and by-pathogen microbiological response at TOC, and clinical response at TOC by resistance genotype will be generated separately from output for final analysis and reported in an addendum to the CSR.

8.8.4 Analysis of Additional Efficacy Endpoints

The per-patient clinical response by pathogen and by-pathogen microbiological response at EOT and TOC will be summarized by resistant pathogen phenotypes (as outlined in Table 6, phenotype categorization for a patient will be determined based on baseline pathogens isolated from urine and/or blood) for the micro-ITT and ME Populations.

In addition, by-pathogen microbiological response at TOC will be summarized by tebipenem MIC and ertapenem MIC for the micro-ITT Population. Similar analyses will be performed each subset of resistant pathogens isolated from urine and/or blood (as outlined in Table 6).

In addition the overall response and per-patient clinical and microbiological response will be summarized for patients with bacteremia at baseline.

8.8.5 Subgroup analyses

Subgroup analyses of the primary efficacy endpoint (overall response at TOC in the micro-ITT Population) will also be conducted. Descriptive statistics along with treatment difference and 95% CI (derived using the unstratified method of Miettinen and Nurminen) will be presented in tables as well as in forest plot for the following subgroups using baseline data:

- Infection category (cUTI, cUTI with/without AP, AP)
- Age category (≥18 to <65 years, ≥65 to <75, ≥75 years)
- Region
- Sex
- Race (Asian/Black or African American/White/Other*)

- Ethnicity (Hispanic or Latino/Not Hispanic or Latino/ Not Reported)
- Creatinine clearance (≤30, >30 to ≤ 50, >50 mL/min)
- Prior antibiotics (Y/N)
- Bacteremia at baseline (Y/N)
- Modified SIRS at baseline (Y/N) **
- Baseline Enterobacterales pathogen susceptibility phenotype (based on the susceptibility of the pathogens isolated from urine and/or blood at baseline and criteria outlined in Table 6; pathogen with highest MIC is considered)
    - ESBL-phenotype baseline pathogens
    - FQ-non-susceptible (NS) baseline pathogens
    - TMP-SMX-resistant baseline pathogens

* Includes 'Other', 'Not Reported', 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' race categories to be combined together for subgroup analysis

** SIRS criteria are modified to consider only temperature, heart rate, respiratory rate, and white blood cells; immature neutrophils counts are not included (as defined in Section 8.7)

8.9 Safety Analysis

All the analyses in this section will be run on Safety Population. No hypothesis testing will be performed; all analyses will be descriptive in nature.

8.9.1 Adverse Events

All AEs will be coded using MedDRA version 21.0 or later. All AEs occurring during this trial for a given patient will be recorded from the first dose of study drug through the late follow-up visit; therefore, all AEs will be deemed as TEAEs.

Summaries of AEs will be provided by treatment and overall for the Safety Population.

An overall summary of AEs will be presented, which will include the number and percentage of patients with at least one TEAE, Serious Adverse Event (SAE), drug-related TEAE, serious drug-related TEAE, TEAE leading to discontinuation from treatment, and TEAE leading to death, along with the total number of events.

The incidence and frequency of TEAEs, SAEs, AEs related to study drug (events classified as possible or probable, or with missing relationship status, will be classified as related to study drug), AEs leading to study drug withdrawal, AEs leading to the study discontinuation, and AEs leading to death will be presented by system organ class (SOC) and preferred term (PT), by treatment and overall. A summary of TEAEs and SAEs by Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) severity grade (severe, life-threatening or disabling and

death) will be presented together in summary tables, by SOC and PT, will also be provided by treatment and overall.

Summaries of TEAEs and SAEs by decreasing frequency of PT for TBPM-PI-HBr and for ertapenem will also be provided by treatment and overall. Based on the latest version of MedDRA, AEs reported due to COVID-19 will be appropriately coded in the listings and identifiable in the summary tables and listings by SOC and PT.

For all summaries, patients will be counted once for each AE category, SOC, or individual AE PT. For the summaries by severity grade, every patient will be counted once for each AE at the highest severity.

Summary tables and listings for TEAEs related to target organ toxicity and for TEAEs of special interest will be provided if deemed appropriate based on the blinded review of the AEs performed by sponsor.

AE summaries will include number of patients with a given AE, as well as number of AEs themselves.

All AE summaries will be repeated summarizing adverse events which occurred starting from first dose to end of treatment visit.

Listings will be provided for all TEAEs, SAEs, TEAEs related to study drug, TEAEs leading to discontinuation from the study, TEAEs leading to study drug withdrawal, and TEAEs leading to death for all patients in the Safety Population. Adverse events of COVID-19 will be coded as a specific preferred term in these listings.

A listing of all deaths, including the date of death and primary cause of death, will be presented for all patients in the Safety Population.

8.9.2 Laboratory Data

Laboratory panels (hematology, chemistry, coagulation, and urinalysis) will be summarized by visit, along with changes from baseline to each post-baseline time point, for each test. All summary tables will be presented by treatment and overall, for the Safety Population. Descriptive statistics will be provided for continuous variables; for categorical variables, number and percentage will be summarized. Only data from the central laboratory will be summarized.

Separate tables will be presented for each laboratory panel.

Shift tables (number and percentage) will be provided by CTCAE 5.0 grades from baseline to the worst post-baseline assessment and will be summarized by treatment and overall for each laboratory test. The number of patients in a particular treatment arm having both baseline and post-baseline results available will be used as the denominator.

Additional analysis of laboratory parameters (chemistry and hematology parameters will be summarized separately) will be conducted in the Safety Population and will include frequencies for worst post-baseline values:

- Patients with at least a 2-grade increase in CTCAE toxicity grade from baseline in any parameters
- Patients with CTCAE toxicity grade ≥ 4 in any parameters

Analysis of patients with post-baseline aminotransferase elevations and total bilirubin by category will be done for worst post-baseline values in the Safety Population and defined as:

  - ALT >3x, >5x, >10x upper limit of normal (ULN)
  - AST >3x, >5x, >10x ULN
  - ALT and AST >3x, >5x, and >10x ULN
  - Total bilirubin >2x ULN
  - ALT and AST >3x ULN *and* total bilirubin >2x ULN

A patient with elevated lab parameters may belong to more than one category (e.g., if a patient has an ALT value = 6xULN, this patient will be presented under both >3xULN and >5xULN).

Patients who meet potential Hy's Law laboratory criteria will be listed. Hy's Law laboratory criteria are defined as any elevated ALT and/or AST of >3xULN that is associated with both an ALP <2xULN and an increase in bilirubin >2xULN.

All laboratory data will be listed for all patients in the Safety Population, including toxicity grades, normal ranges, and clinically significance flags; values outside their normal range will be flagged as H (high, above normal) or L (low, below normal).

A listing of all pregnancy test results will be provided for all female patients in the Safety Population, where applicable.

Box plots of laboratory values (ALT, AST, bilirubin, GGT, hematocrit, platelets, neutrophils, WBC, differential counts, total/free carnitine, BUN, creatinine, calcium, total/direct bilirubin, hemoglobin) versus visit will also be provided by treatment group.

8.9.3 Vital Signs and Other Safety Endpoints

Vital signs include systolic and diastolic blood pressure (mmHg), weight (kg), pulse rate (beats per minute [bpm]), respiratory rate (breaths per minute), and maximum daily temperature (degree C).

Summary tables of vital signs observed values and changes from baseline to scheduled post-baseline visits will be presented by treatment and overall, for the Safety Population, for each vital sign collected. Similar tables will be created for each ECG parameter. When ECG data are collected in triplicates, the average value among three measurements will be summarized.

Electrocardiogram summaries include heart rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec), RR interval (msec), QTcF interval (msec).

Electrocardiogram values (the worst interpretation value of the triplicate) will be summarized by the number and percentage classified as normal, abnormal – not clinically significant, abnormal – clinically significant, or not done at each scheduled visit, by treatment and overall, for the Safety Population.

Worst post-baseline categorized QTcF values will be presented in the Safety Population as follows:

- QTcF >500 msec and baseline ≤500 msec
- QTcF >480–≤500 msec and baseline ≤480 msec
- QTcF >450–≤480 msec and baseline ≤450 msec
- QTcF change from baseline >30–≤60 msec
- QTcF change from baseline >60 msec
- Post-baseline QTcF >500 msec and QTcF change from baseline >30–≤60 msec
- Post-baseline QTcF >500 msec and QTcF change from baseline >60 msec
- Post-baseline QTcF >480–≤500 msec and QTcF change from baseline >30–≤60 msec
- Post-baseline QTcF >480–≤500 msec and QTcF change from baseline >60 msec

Listings of vital signs data and ECG data (observed and change from baseline) will be presented for all patients in the Safety Population; the listings will state all parameters in their original collection units.

Abnormal physical examination (PE) results will be recorded at baseline and will be listed. Post-baseline abnormal PE values will be recorded as AEs and summarized and listed as AEs. No specific summaries for the PE values will be created.

Urinary tract signs and symptoms (term and severity) will be listed and also summarized by visit in the Safety Population.

8.9.4 Exposure to Study Drug

The following parameters will be calculated for the exposure data:

- Actual total IV dose (in mL) received throughout the study, defined as the sum of all the IV doses received by the patient.
- Actual total oral dose received throughout the study (mg), defined as the sum of all the oral doses received by the patient.
- Duration of the IV treatment (days), defined as (number of hours between last and first injection + 1)/ 24 hours.

- Duration of the oral treatment (days), defined as (number of hours between last and first oral intake + 1)/ 24 hours.
- Compliance will be defined separately for oral and IV drug. Compliance for oral drug will be calculated as actual number of tablets taken/planned number of tablets. Actual number of tablets = all tablets taken by a patient. Planned number of tablets will be calculated as a sum of all planned doses per intake for a patient. Planned dose per intake will be 2 or 1 (if creatinine clearance values require dose adjustment as recorded on CRF data). Compliance with IV drug will be defined in a similar way.

The above-defined parameters will be summarized in the Safety Population by treatment arm. Duration of the IV and oral treatment will be summarized both categorically and using means. Compliance will be summarized as a continuous variable.

Listings will be created for all oral and IV doses administered and compliance (oral and IV).

8.10 Other Endpoints

8.10.1 Pharmacokinetic Data

Descriptive statistics of individual plasma concentrations for TBPM will be summarized and listed according to the nominal sampling windows post dosing for the PK Population and will be reported in the CSR. Summaries for PK plasma concentration will include n, mean, standard deviation, minimum, maximum, median as well as geometric mean and coefficient of variation, TBPM blood concentrations were converted to plasma concentrations using the following equation: TBPM plasma concentration = reported blood concentration x 3.6; where 3.6 represents a product of hematocrit value of 1.8 and dilution factor of 2 by addition of 1:1 isopropyl alcohol (IPA): Blood volume. IPA was added as a stabilizer during blood sample collections to prevent conversion of TBPM-PI to TBPM post sample collection. TBPM compartmental pharmacokinetic (PK) parameters derived from Population PK analysis, and potential PK/pharmacodynamic (PD) relationships will be reported separately.

9. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

The following updates were made to the planned analysis:

- The definition of sustained clinical cure at LFU was clarified, in that a patient should meet criteria for clinical cure at TOC and remain free of *new* signs and symptoms of cUTI or AP at LFU.
    - Justification: Some signs and symptoms may be minimal and not require therapy at LFU, and the patient is still a sustained cure without the need for rescue antibiotics. The intent of the protocol was to use the term “new” signs and symptoms for sustained cure at LFU, to ensure a consistent approach to the

handling of "new" signs and symptoms as they are defined for success and failure at LFU.

- The definition of micro-ITT Population was modified to exclude patients who have non-fermenting Gram-negative bacilli, MRSA and/or pathogens non-susceptible to meropenem.
    - Justification: The intent is to exclude the totality of pathogens not expected to respond to study drugs including carbapenemase-producing *Enterobacterales* using meropenem as the most appropriate surrogate for resistance via carbapenemase production.
- The definition of the micro-ITT Population was clarified to note that patients with one or more uropathogens isolated from blood at baseline/Screening would be included in the micro-ITT Population as outlined in the ERP (v.3 dated 20 Aug 2020).
    - Justification: Language clarified to be consistent with the industry study standard and the approach followed throughout the study as documented in the ERP v.3 dated 20 Aug 2020 and DRC meeting minutes. In order to ensure transparency, the clarification provided in these documents was also added to the SAP definition.
- The definition of baseline culture or baseline pathogen was updated to note that the baseline pathogen could be identified from any culture collected within 48 hours prior to the first dose or post-dose if on the same calendar day as day 1.
    - Justification: It would be inappropriate to exclude a pathogen isolated at the required $>10^5$ CFU/ml on the same calendar day as the start of study therapy.
- Presentations for overall response at EOT will be provided in the micro-ITT and ME Populations, and presentations of clinical cure at EOT and TOC by baseline pathogen will be provided in the micro-ITT and ME Populations.
    - Justification: These additional data are to be presented to provide a complete review of the clinical trial results for the key endpoints at key time points.
- Definitions of the CE and ME Populations were clarified to include by-visit CE and ME Populations, and criteria for inclusion in these populations were also updated.
    - Justification: The patients included in the CE and ME Populations will vary by visit as this will depend upon the data available.
- Protocol requires demographics and baseline characteristics to be summarized in ITT and Safety Populations; however, the ITT Population will not be used.
    - Justification: The Safety Population is used to support safety summaries, whilst the ITT Population is not required as this will be a very similar population.

- Pathogen summaries for *Enterobacteriaceae* have been updated to the order "*Enterobacterales*" based on current taxonomy.
    - Justification: *Enterobacterales* is the current appropriate taxonomic term for this group of bacteria.
- Day 5 microbiological response rates by-pathogen were removed from the Day 5 exploratory endpoint.
    - Justification: The intent was to provide an overall per-patient assessment and the outcomes by-pathogen are likely to be non-meaningful at Day 5 and unlikely to be different than the analysis of by-pathogen outcomes at EOT.

10. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the Sponsor company and protocol number will be presented. On the next line, a table/listing number followed by the title of the table/listing and population information will be displayed. Horizontal lines will appear after the column heading of the table/listing. Footnotes will be put under the main body of text at the bottom of the page.. The source listing number and the ADaM dataset used, along with the date of the data snapshot or the date of database lock, will be displayed for all tables. The SAS program name (including location) and the programmer ID will appear bottom left in a string, and the date and time of creation of table/listing will appear bottom right. The page number will appear on the top right corner of each table/listing.

Courier New 8-point bold font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9 format (DDMMMYYYY).

11. TABLES, LISTINGS, AND FIGURES

The TLFs will be provided in a separate Mock-Up TLFs document, which will be finalized separately from this SAP.

12. 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[s]			X	X	X
Focused Physical Examination [e]		X	X			
Vital Signs (T, P, RR, BP) [f]	X[s]	X	X	X	X	X
Collection of cUTI/ AP signs and symptoms	X[s]	X[r]	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[s]	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[s]	<----------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 Protocol 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 Protocol 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 are intended to occur within the first 8 hours after dosing
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.