Official Title:	**A Phase 3, randomized, double-blind, double-dummy, multicenter, multinational study to assess the efficacy and safety of orally administered tebipenem pivoxil hydrobromide (TBP-PI-HBr) compared to intravenously administered imipenem-cilastatin in patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP)**
NCT Number:	**NCT06059846**
Document Date:	**Statistical Analysis Plan Version 2: 17 March 2025**

STATISTICAL ANALYSIS PLAN

Investigational Product: **Tebipenem pivoxil hydrobromide (TBP-PI-HBr, previously known as SPR994)**

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

Protocol, Version: **SPR994-305, V4.1**

Short Title: **PIVOT-PO**

Sponsor Legal Registered Address:

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Regulatory Agency Identifier Number(s)

Registry	ID
EU CT Number	2023-503785-22-00

Statistical Analysis Plan Version: **V2 17 Mar 2025**

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Confidential Information

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VERSION HISTORY

Table 1 documents the changes to the Statistical Analysis Plan (SAP).

Table 1: SAP Version History Summary

SAP Version Approval Date	Rationale	Changes to SAP
V1 3 Apr 2024	Original version	Not Applicable
V2 17 Mar 2025	For accuracy and clarity of content	Title and Signature pages: Updated protocol version to V4.1. Abbreviations/Definitions, Table 2 and Table 8, and Appendix 1: Revised FQ-NS definition from fluoroquinolone-nonsusceptible to fluoroquinolone-not susceptible. Section 3 and Section 4.4.3: Removed reference to "qualifying". Section 4.1.4: Updated the Baseline definition to use the standard definition for Baseline pathogen rather than an alternative. Section 4.1.5-Table 8: Revised extended spectrum ß-lactamase (ESBL)-phenotype definition for *Proteus mirabilis* to use cefotaxime instead of ceftriaxone. Clarified medications used for multi-drug resistant definition. Section 4.2: Added list of regions. Section 4.4.3: Updated "nonsusceptible" to "not susceptible". Clarified list of tables for in vitro testing results of Baseline pathogen susceptibility. Clarified counting convention wording for summary of Baseline pathogen susceptibility phenotypes on a per-patient basis. Section 4.6: Revised compliance calculation to use actual/planned number of doses rather than tablet counts. Section 4.7.4 and Section 4.8.3: Clarified primary and secondary efficacy data will be listed for the Intent-to-Treat (ITT) Population, with a flag to denote patients included in the microbiological ITT (micro-ITT), Extended micro-ITT, and Gram-positive (GP) populations. Section 4.10.2: Added reference to derivation of corrected calcium and production of a box plot. Appendix 2: Made minor wording updates to Schedule of Assessments footnotes to align with protocol amendment. Appendix 3, contaminant bullet 2: Clarified that *Corynebacterium* spp. is a contaminant, with the exception of *Corynebactrium urealyticum.*
	Updated text to reflect the administrative decision to pause enrollment while the Interim Analysis (IA) is being prepared. This has no impact on primary analysis or patient safety.	Section 2.4.1: Deleted following original text: "During the IA, the accrual of the study will continue. If efficacy success (i.e., NI) is reached at the IA and the study is stopped early, the IA will be the primary analysis and data collected between the IA data cut and the time when the study is stopped will be considered overrun. Overrun

SAP Version Approval Date	Rationale	Changes to SAP
		data will be pooled with the IA data to repeat the primary efficacy analysis as a sensitivity analysis. Output generated after stopping will be based on all data collected (IA+overrun). Any displays generated for IA will be repeated based on all data collected (IA+overrun)." Replaced above text with: "The enrollment will be paused for all sites during the preparation for IA. The IA will comprise all patients enrolled up to the IA enrollment cut-off. Hence, there will be no overrun, if the study is stopped for efficacy success."
	Population criteria for IA Set not needed given the enrollment pause during IA preparation, with the analysis comprising patients enrolled up to the IA enrollment cut-off	Section 3: Deleted references to IA Set
	Populations added to support the breakpoint package for submission	Section 3: Added Extended micro-ITT and Extended Microbiologically Evaluable (ME)- Test-of-Cure (TOC) Populations. To be used for supplemental outcome-by-minimum inhibitory concentration (MIC) analyses. Section 4.7.5 and Section 4.8.4: Added summaries of overall, clinical, and per-pathogen microbiological responses at TOC by tebipenem MICs for Baseline pathogens isolated from urine and/or blood in the micro-ITT and Extended micro-ITT Populations.
	The Clinically Evaluable (CE)-TOC Population includes patients without a Baseline pathogen, thus overall response (that includes microbiological response as a component) should not be evaluated in this population.	Section 4.7.4: Removed the supplementary analysis of overall response in the CE-TOC Population.
	To ensure all patients with liver abnormalities are evaluated	Section 4.10.2: Removed the criterion that patients have a normal baseline to be included in the summary of post-Baseline aminotransferase and total bilirubin elevations.
	Search terms added to provide more specificity for adverse events of special interest	Appendix 4 and Appendix 5: Added terms.

ABBREVIATIONS/DEFINITIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AP	acute pyelonephritis
AST	aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
β-HCG	beta human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
° C	degrees Celsius
CDISC	Clinical Data Interchange Standards Consortium
CE	Clinically Evaluable
CFU	colony forming unit
CI	confidence interval
CLSI	Clinical and Laboratory Standards Institute
Cr	creatinine
CrCl	creatinine clearance
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
cUTI	complicated urinary tract infection
DMP	Data Management Plan
[redacted]	[redacted]
eCRF	electronic case report form
ECG	electrocardiogram
EOT	End-of-Treatment
ERP	Evaluability Review Plan
ESBL	extended spectrum ß-lactamase
EU	European Union
FOCP	female of childbearing potential
FQ-NS	fluoroquinolone-not susceptible

Abbreviation	Definition
FQ-S	fluoroquinolone-susceptible
GP	Gram-positive
GS	Gram stain
h	hour
HLT	high level term
IA	interim analysis
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IP	investigational product
ITT	Intent-to-Treat
IV	intravenous(ly)
KM	Kaplan-Meier
LE	leukocyte esterase
LFU	Late Follow-Up
MDR	multidrug-resistant
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MIC	minimum inhibitory concentration
micro-ITT	microbiological Intent-to-Treat
min	minutes
MLST	multi-locus sequency typing
NI	non-inferiority
PDF	portable document format
PI	principal investigator
PK	pharmacokinetic(s)
PO	orally
PT	preferred term
QTcF	Fridericia-corrected QT interval
qXh	every X hours
RBC	red blood cells
SAE	serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SD	standard deviation
SDTM	Standard Data Tabulation Model
SIRS	systemic inflammatory response syndrome
SMQ	standardized MedDRA queries
SOC	system organ class
TBP	tebipenem
TBP-PI-HBr	tebipenem pivoxil hydrobromide
TEAE	treatment-emergent adverse event
TLFs	tables, listings, figures
TMP-SMX-R	trimethoprim-sulfamethoxazole-resistant
TOC	Test-of-Cure
UC	urine culture
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cells
WHO	World Health Organization

SAP APPROVAL SIGNATURE PAGE

PROTOCOL TITLE	**A Phase 3, randomized, double-blind, double-dummy, multicenter, multinational study to assess the efficacy and safety of orally administered tebipenem pivoxil hydrobromide (TBP-PI-HBr) compared to intravenously administered imipenem-cilastatin in patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP)**
SAP Version, Date	V2, 17 Mar 2025
SAP AUTHOR	[redacted] EMB Statistical Solutions, LLC Signed by: [redacted] Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 18-Mar-2025 | 12:43:45 PM EDT Date: [redacted] 18-Mar-2025
Investigational Product	Tebipenem pivoxil hydrobromide (TBP-PI-HBr)
Protocol Number	SPR994-305
Protocol Version, Date	V4.1, 26 Aug 2024
Signature Statement	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Reviewers on behalf of Spero Therapeutics, Inc.

Approver Signature	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 18-Mar-2025 | 12:15:54 PM EDT Date: 18-Mar-2025
[redacted] PhD Spero Therapeutics, Inc.	
Approver Signature	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 18-Mar-2025 | 1:37:59 PM EDT Date: 18-Mar-2025
[redacted] MD Medical Monitor Spero Therapeutics, Inc.	
Approver Signature	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I have reviewed this document Signing Time: 18-Mar-2025 | 12:14:46 PM EDT Date: 18-Mar-2025
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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the analysis variables and statistical procedures that will be used to analyze and report the results from study protocol SPR994-305. This is a Phase 3, randomized, double-blind, double-dummy, multicenter, multinational study to assess the efficacy and safety of orally (PO) administered tebipenem pivoxil hydrobromide (TBP-PI-HBr) compared to intravenously (IV) administered imipenem-cilastatin in patients with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP).

In addition, pharmacokinetics (PK) of tebipenem will be characterized in the target population. Details of the PK analyses will be addressed in a separate analysis plan.

This SAP was written in accordance with the recommendations outlined in the International Council for Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports". The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

If, after the study has begun, changes are made to the primary endpoint of the study, the protocol will be amended. If the statistical methods related to those primary hypotheses are amended, this will either be documented via a protocol amendment or explicitly stated in the SAP.

Some of the analyses detailed here may be more explicit or in some respects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol, and the differences will be presented in Section 4.12.

Changes to the protocol that impact the design, the data collected, or the statistical methods that occur after the finalization of this SAP may require amendment of the approved SAP. Similarly, changes to the planned analysis variables and/or statistical methods described in the approved SAP may also require amendment of the SAP, so long as the changes are implemented prior to unblinding. Changes in planned analyses that are decided after unblinding will be documented in the Clinical Study Report (CSR).

The formats for the Tables, Listings, and Figures (TLFs) described in this SAP will be provided in a companion document. Changes to the formats of these TLFs that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or [redacted] requested after SAP approval will not require amendment of the SAP and will instead be described in the CSR.

Please see the study protocol and laboratory manual for details about the study design, procedures, and schedule of assessments and see the electronic case report form (eCRF) for details about variables collected and their possible values.

1.1. Objectives, Endpoints, and Estimands

The study objectives and endpoints are outlined in Table 2.

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to the overall response (combined clinical cure plus microbiological eradication) at the TOC visit in hospitalized adult patients (≥18 years of age) with cUTI/AP	Overall response (combined per-patient clinical cure and favorable microbiological response) at the TOC visit in the micro-ITT Population, as defined by: a. clinical cure: complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at Baseline and no new symptoms, such that no further antimicrobial therapy is warranted, and patient is alive b. favorable microbiological response (microbiological eradication): reduction of Baseline uropathogens to $<10^3$ CFU/mL and negative repeated blood culture if blood culture was positive for uropathogen growth at Baseline and patient is alive
Secondary	
1. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall response rates at the TOC visit in patients with cUTI/AP in the Microbiologically Evaluable (ME) Population	1. Overall response at the TOC visit in the ME Population
2. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall response rates at the EOT and LFU visits in patients with cUTI/AP	2. Overall response at the EOT and LFU visits in the micro-ITT and ME Populations
3. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to clinical response rates at the EOT, TOC, and LFU visits in patients with cUTI/AP	3. Clinical response at the EOT, TOC, and LFU visits in the micro-ITT, CE, and ME Populations
4. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to microbiological response rates at the EOT, TOC, and LFU visits in patients with cUTI/AP	4. Microbiological response at the EOT, TOC, and LFU visits in the micro-ITT and ME Populations
5. To assess the efficacy of oral TBP-PI-HBr as compared with IV imipenem-cilastatin with respect to overall, clinical, and microbiological response rates at the TOC, EOT, and LFU visits among cUTI/AP patients infected with drug-resistant Enterobacterales uropathogens, e.g., ESBL-producing, FQ-NS, and/or TMP-SMX-R strains	5. Overall, clinical, and microbiological response at the TOC, EOT, and LFU visits in the micro-ITT and ME Populations in patients with drug-resistant Enterobacterales
6. To assess the safety and tolerability of oral TBP-PI-HBr as compared to IV imipenem-cilastatin in patients with cUTI/AP	6. TEAEs and SAEs and change from Baseline results for clinical laboratory tests, ECGs, and vital sign measurements in the Safety Population

Objectives	Endpoints
7. To provide TBP plasma concentration data to characterize the PK of TBP in the target population using PK modelling	7. TBP plasma concentration in the TBP PK Population

[redacted]

AP, acute pyelonephritis; CE, Clinically Evaluable; CFU, colony forming unit; cUTI, complicated urinary tract infection; [redacted] ECGs, electrocardiograms; EOT, End-of-Treatment; ESBL, extended spectrum β-lactamase; FQ-NS, fluoroquinolone-not susceptible; IV, intravenous; LFU, Late Follow-up; ME, Microbiologically Evaluable; micro-ITT, Microbiological Intent-to-Treat; mL, milliliter; PK, pharmacokinetic; SAE, serious adverse event; TBP, tebipenem; TBP-PI-HBr, tebipenem pivoxil hydrobromide; TEAE, treatment-emergent adverse event; TMP-SMX-R, trimethoprim-sulfamethoxazole-resistant; TOC, Test-of-Cure.

1.1.1. Primary Objective and Estimand

Primary Objective:

See Table 2 above.

Primary Estimand:

The primary clinical question of interest is: What is the treatment effect with respect to the overall response at the TOC visit following treatment with oral TBP-PI-HBr 600 milligrams (mg) every 6 hours (q6h) compared to IV imipenem-cilastatin 500 mg q6h, each administered over 7-10 days duration, in patients with cUTI or AP due to qualifying uropathogens, regardless of treatment discontinuation for any reason?

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

The primary estimand is described by the following attributes:

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

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

The rationale for the primary estimand includes:

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

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

Use of non-study systemic antimicrobial agents for infections other than cUTI/AP should be restricted to agents without anticipated activity against the Baseline pathogen whenever possible. Therefore, a favorable overall response precludes the use of other potentially effective systemic

antimicrobials with potential activity against the Baseline pathogen(s) when initiated for the treatment of the index infection (cUTI/AP).

1.1.2. Secondary Objectives and Estimands

Secondary Objectives:

See Table 2 above.

Secondary Estimands:

Efficacy:

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

Receipt of non-study systemic antimicrobials impacts the endpoint outcome definitions (see Section 1.1.1).

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

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

Safety:

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

PK:

The TBP plasma concentrations will be assessed to inform population PK modeling and will be separately reported.

Refer to Appendix 1 for the components of estimand for the secondary endpoints.

1.2. Study Design

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

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

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

- Imipenem-cilastatin 500 mg, administered IV over 30 min q6h (±1 h) plus matched dummy tablets administered PO q6h (±1 h)

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

Randomization will be stratified by age at time of consent (≥18 to <65 years vs. ≥65 years), baseline diagnosis (cUTI vs. AP), and presence or absence of urinary tract instrumentation at Baseline.

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

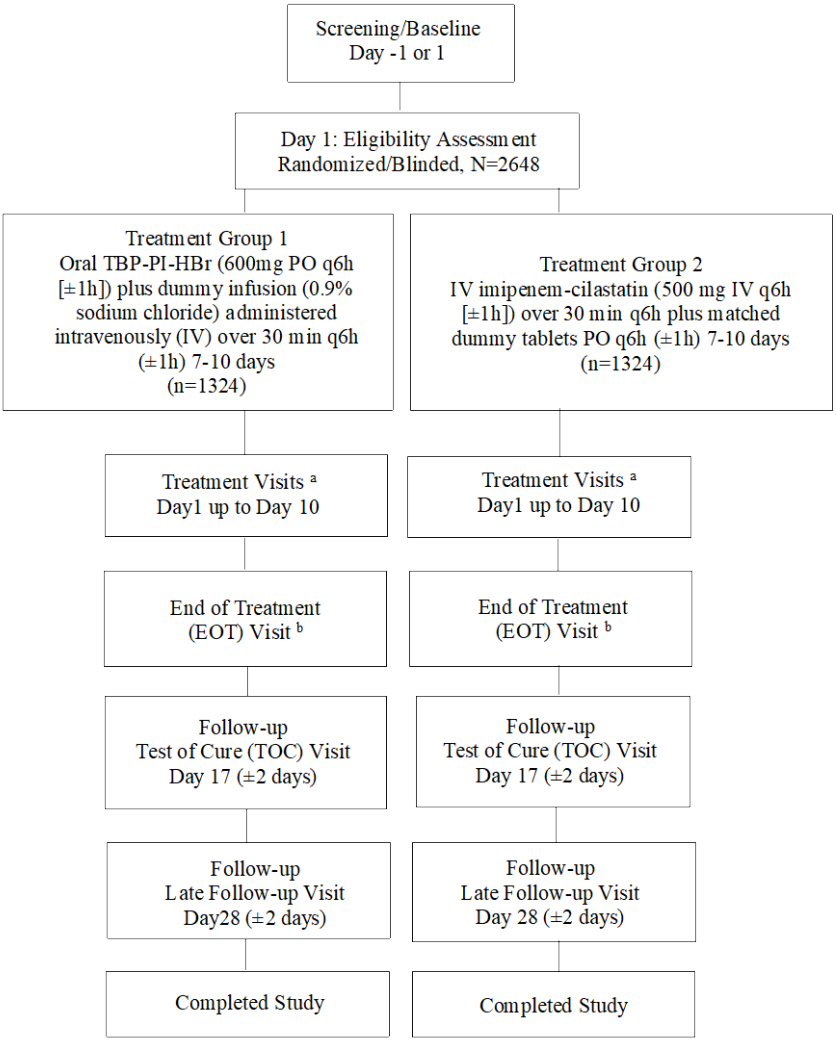
Refer to Figure 1 for a study design flow chart and to Appendix 2 for a schedule of assessments.

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

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

The study plans to enroll approximately 2648 patients (1324 per treatment group) at up to 160 clinical centers to achieve a target sample size of approximately 1588 evaluable patients (794 per treatment group) for the primary analysis population (micro-ITT Population) which would provide 89% power with a one-sided significance level of 0.025 for assessment of non-inferiority (NI) of oral TBP-PI-HBr to IV imipenem-cilastatin using a -10.0% NI margin (refer to Section 2.2.1). The final number of randomized patients will depend on a planned IA to be performed when 60% of the patients in the micro-ITT Population (approximately 954 patients) have response data available at the TOC visit, potentially allowing for early termination of the study based on certain pre-specified criteria (refer to Section 2.4.1).

Figure 1: Study Design Flow Chart



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

2. STATISTICAL HYPOTHESES AND TESTING

The statistical hypotheses corresponding to the primary estimand are provided below. Formal hypothesis testing for the secondary estimands will not be performed.

2.1. Statistical Hypotheses

The study is designed to determine whether TBP-PI-HBr, administered PO is non-inferior compared to intravenously administered imipenem-cilastatin with respect to the primary efficacy endpoint of overall response (combined per-patient clinical cure and favorable microbiological response) at the TOC visit in the micro-ITT Population.

The null and alternative hypotheses corresponding to the primary estimand (see Section 1.1.1) are the following:

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

$H1: P1 - P2 > -\Delta$

Where:

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

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

Δ = 10 % the NI margin

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

$H0: P1 - P2 \leq 0$

$H1: P1 - P2 > 0$

Where:

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

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

One IA with stopping rules for both efficacy and futility will be performed. At the IA, if the Z statistic (for the primary analysis population [micro-ITT Population]) is higher than the Z statistic boundary for NI, the study will be stopped for efficacy and NI will be declared. Superiority will then be tested. If the one-sided p-value is less than the p-value boundary for NI, superiority of TBP-PI-HBr will be declared. See Section 2.4.1 for details on futility stopping rules. The futility bounds of this study are nonbinding and are considered guidance rather than strict bounds.

At the final analysis (if the study continues at the IA), if the Z statistic (for the primary analysis population [micro-ITT Population]) is higher than the Z statistic boundary the study will be declared successful, and NI will be declared. Superiority will then be tested. If the one-sided p-value is less than the p-value boundary, superiority of TBP-PI-HBr will be declared.

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

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

2.2. Sample Size Determination

2.2.1. Justification of Sample Size

Patients will be randomized to TBP-PI-HBr and imipenem-cilastatin in a 1:1 ratio. Assuming a 60% overall response rate for imipenem-cilastatin and 58% overall response rate for

TBP-PI-HBr, a sample size of approximately 1588 patients in the micro-ITT Population is required, for a design with one IA at 60% information fraction and allowing for stopping the study based on efficacy or futility, to provide 89% power to demonstrate NI in the overall response rate of TBP-PI-HBr and imipenem-cilastatin with a 0.025 one-sided alpha level and a -10.0% NI margin. The minimal response rate difference that is estimated to meet the statistical criterion for NI is provided in Table 3.

Table 3: Estimated Minimal Response Rate Difference for Efficacy and Futility Interim Analysis

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

micro-ITT, microbiological Intent-to-Treat.

The study is planned to enroll approximately 2648 patients (1324 per treatment group) to ensure a sufficient number of patients in the primary analysis population (micro-ITT Population) assuming a 60% evaluability rate. The final number of randomized patients may vary based on the evaluability rate for the micro-ITT Population.

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

2.2.2. Sample Size Sensitivity

Sensitivity of the sample size has been explored considering various overall response rates. Table 4 and Table 5 display the minimum power under various assumptions of "true" therapeutic success rates of TBP-PI-HBr and imipenem-cilastatin under different IA designs, when the IA is conducted at approximately 60% information fraction of the design allowing for efficacy and futility stop at the IA. For all of these cases, the one-sided type I error is 0.025, the NI margin is -10.0%.

Table 4: Power of the Study Under Various Assumptions of the True Therapeutic Success Rates for Efficacy and Futility Group Sequential Design

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

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

[a] Number of Patients is rounded up to even numbers.
TBP-PI-HBr, tebipenem pivoxil hydrobromide.

Table 5: Impact of Evaluability Rate on ITT Population

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

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

2.3. Multiplicity Adjustment

The primary comparison of interest is the comparison of TBP-PI-HBr to imipenem-cilastatin for the primary endpoint of overall response rate at the TOC visit in the micro-ITT Population. This analysis will be adjusted for stratification factors. The issue of multiple comparisons in the primary analysis will be addressed by testing the noninferiority of TBP-PI-HBr to treatment with imipenem-cilastatin prior to testing for superiority as described in Section 2.1.

There will be no multiplicity adjustment for the testing of the secondary endpoints, since no formal hypothesis testing will be performed.

2.4. Planned Analyses

2.4.1. Interim Analysis and Independent Data Monitoring Committee

One IA is planned to assess both efficacy and futility by the Independent Data Monitoring Committee (IDMC), as well as review safety data. The IDMC will meet when approximately 954 patients in the micro-ITT Population (60% of the maximum planned 1588 patients in the micro-ITT Population) have achieved the TOC visit to evaluate the primary endpoint, identify potential treatment benefit, review safety data, and make recommendations for continuing or stopping the study, as per the IDMC charter. The IDMC can also be convened on an ad hoc basis if the blinded study team identifies a potential safety signal and escalates this to the IDMC to review unblinded data for further evaluation. The IDMC members will include at least five independent experts, including an infectious disease clinician, a chairperson with experience

chairing IDMC meetings, a clinical microbiologist, and a statistician with infectious disease experience. Details regarding the IDMC process will be described in the IDMC charter.

An independent unblinded statistical team will conduct and provide all unblinded analyses to the IDMC before the meeting is held. Details on the content and structure of the data output will be described in a separate IA SAP, including summaries of the following data:

- Study population (patient disposition, study treatment status and reasons for discontinuation, study populations, demographics and other Baseline characteristics, and Baseline disease characteristics)
- Efficacy endpoints (overall response, clinical response, and microbiological response at the TOC visit)
- Safety endpoints (overall summary of AEs, AEs/SAEs by system organ class and preferred term, listing of fatal/non-fatal SAEs, related AEs/SAEs, AEs leading to treatment discontinuation, and AEs of special interest).

Study team members from the Sponsor and contract research organization (CRO) who are directly involved in the study and conducting the final analysis will remain blinded. The IDMC and independent team will maintain unblinded data in a secure area to ensure the integrity of the data until the study is completed. Details on protecting the blind and data integrity will be described in a blinding plan.

An IA with stopping rules for both efficacy and futility will be performed. The nominal significance levels for the interim and final analyses will be determined using Rho (ρ) family error spending boundaries (Jennison 2000), given by $f(t) = \alpha t^{\rho}$, where α is the overall significance level. The stopping boundary for assessing efficacy at interim will use rho=2 and a (non-binding) stopping rule for futility at interim will use rho=3. The futility bounds of this study are nonbinding and are considered guidance rather than strict bounds.

The rho values were selected to give the desired study operating characteristics. See Table 6 for a summary of the information fraction, sample size, and decision guidance (boundaries in Z statistics and p-value, cumulative Alpha, and Beta) for the planned IA at approximately 954 patients (which is 60% information fraction of the micro-ITT Population) with a 0.025 one-sided overall Type I Error and a 0.114 overall Type II Error approximately.

Table 6: Information Fraction and Stopping Boundaries for Efficacy and Futility Interim Analysis

Information Fraction	Target Sample Size for Study	Efficacy Boundary			Non-Binding Futility Boundary		
		Z Statistic	P-Value	Cumulative Alpha	Z Statistic	P-Value	Cumulative Beta
60%	954	>2.365	<0.009	0.009	<0.544	>0.293	0.025
100%	1588	>2.039	<0.021	0.025	≤2.039	≥0.021	0.114

Note: Testing for noninferiority and superiority share the same Z statistic and p-value boundaries.

The efficacy boundaries and futility boundaries in Table 6 at the IA are based on 60% information fraction of the micro-ITT Population. The actual boundaries will be determined from

the actual number of patients in the micro-ITT Population at the time of the IA using rho family error spending boundaries.

During the IA, if efficacy success (i.e., NI) is reached, a one-sided p-value for testing superiority (see Section 2.1) will be calculated using the same method and compared against the p-value boundary for efficacy.

The enrollment will be paused for all sites after the IA enrollment cut-off and during the preparation for IA. The IA will comprise all patients enrolled up to the IA enrollment cut-off. Hence, if the study is stopped for efficacy success there will be no overrun. If efficacy success is not reached as assessed by the IDMC at the IA and there are no reasons to stop the study early based on safety concern(s) or futility, the study will continue enrollment to the maximum target sample size for the micro-ITT Population of approximately 1588 patients.

Details for the IA are described in the IDMC charter and a separate IA SAP. In particular, blinded study team members will remain blinded until all patients have completed the study, data are cleaned, and final database lock has occurred.

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

2.4.2. Final Analysis

If the study is not stopped for success at the IA, all analyses will be performed on all patient data after study completion. The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All patients have completed the study as defined in the protocol at the LFU visit.
2. All protocol deviations are captured and categorized, and analysis populations defined.
3. All final database cleaning and data lock activities are completed by data management.
4. All criteria for the unblinding of patient randomization codes have been achieved.
5. All randomization codes have been distributed per standard operating procedures.

3. 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 IP or comparator. Patients will be summarized by the treatment to which they were randomized.
- **Safety Population**: Randomized patients who received any amount of IP or comparator. Patients will be summarized by the treatment which they received.
- **Microbiological Intent-to-Treat (micro-ITT) Population**: All randomized patients (using treatment as randomized) who have all of the following:

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

  Note: If a patient is coinfected with two uropathogens, imipenem must have antibacterial activity against both pathogens.
- no more than two microorganisms identified in the baseline urine culture, regardless of colony count.

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

- **Clinically Evaluable (CE) Population:** Three CE Populations will be defined – at EOT (CE-EOT), TOC (CE-TOC), and LFU (CE-LFU). The CE Populations include patients who meet the definition for the ITT Population and have no important protocol deviations or meet other criteria that would affect the assessment of efficacy including:
  - A minimum of eight doses of study drug (or <8 doses if discontinued due to an adverse event [AE] or death)
  - Treatment compliance ≥80% of expected number of doses
  - Had an outcome assessed as clinical cure or clinical failure at the respective EOT, TOC, or LFU visit
  - Had an appropriate diagnosis of cUTI/AP based on Inclusion Criteria 4 (cUTI/AP definition), Inclusion Criteria 5 (pyuria documentation), and Exclusion Criteria 1e (no confirmed or suspected acute or chronic bacterial prostatitis, orchitis, or epididymitis)
  - Did not violate criteria surrounding use of prior antibiotics (i.e., Exclusion Criterion 7)
  - Did not receive a concomitant systemic antimicrobial with potential activity against any of the Baseline pathogens between the time of randomization and EOT, TOC, and LFU, respectively, except therapies used to treat cUTI/AP or complications in patients who have failed therapy. Whether an antimicrobial had

the potential to treat the Baseline pathogens will be determined by the evaluability review team as outlined in the Evaluability Review Plan (ERP)

- Study personnel (site, Sponsor, and CRO) involved in execution of trial and/or patient assessment remained blinded up to and including the relevant visit
- Had a clinical assessment performed within the respective protocol defined visit window
- Other confounding factors that could interfere with the assessment of the primary outcome including but not limited to exclusion criteria violations, unrecognized prohibited conditions present at Baseline, and other events identified by a blinded evaluability review team prior to database lock.

- **Microbiologically Evaluable (ME) Population:** Three ME Populations will be defined – at EOT (ME-EOT), TOC (ME-TOC), and LFU (ME-LFU). The ME Populations include patients who meet the definition for both the micro-ITT and CE Populations. In addition, to be included in the ME Population, patients must not have a microbiological outcome of indeterminate for the applicable visit.
- **Gram-positive (GP) Population:** All patients in the ITT Population (using treatment as randomized) with a baseline urine culture demonstrating $\geq 10^5$ CFU/mL of *E. faecalis, S. aureus,* and/or *S. saprophyticus* (or the same pathogen is present concurrently in blood cultures and in urine) against which imipenem has antibacterial activity AND no more than two microorganisms are identified in the urine culture regardless of colony count. Additionally, if a patient has more than one pathogen identified, the second pathogen must be *E. faecalis, S. aureus, S. saprophyticus*, or an Enterobacterales spp. (see micro-ITT Population description above for the definition of antibacterial activity). This population will be used for supplemental analysis of the treatment effect for these Gram-positive pathogens.

  Note: For *E. faecalis*, antimicrobial activity will be presumed where the ampicillin MIC is ≤8 µg/mL. For *S. aureus*, antimicrobial activity will be presumed where the oxacillin MIC is ≤2 µg/mL. For *S. saprophyticus*, antimicrobial activity will be presumed where the oxacillin MIC is ≤0.5 µg/mL.
- **PK Population:** All patients treated with at least one relevant dose of TBP-PI-HBr with at least one quantifiable plasma or [redacted] sample according to the subpopulations outlined below:
  - **Intensive Plasma PK Subgroup**: approximately 20 TBP-PI-HBr-treated patients who separately consent to optional intensive blood sampling with at least one quantifiable plasma PK sample
  - **Sparse Plasma PK Subgroup**: all remaining TBP-PI-HBr-treated patients designated for sparse sampling with at least one quantifiable plasma PK sample
  - [redacted]

  Further details will be provided in a separate PK Analysis Plan.

The following extended analysis populations will be used to support the breakpoint package for submission:

- **Extended micro-ITT Population**: All randomized patients (using treatment as randomized) who have all of the following:
  - A baseline urine culture demonstrating ≥10^5 CFU/mL of a uropathogen (Enterobacterales species*, Enterococcus faecalis, Staphylococcus aureus*, or *Staphylococcus saprophyticus*) regardless of susceptibility to imipenem or its surrogate (for Gram-positive organisms) OR the same pathogen present concurrently in blood cultures and in urine.
  - No additional pathogens other than an additional Enterobacterales species, *E. faecalis*, *S. aureus*, or *S. saprophyticus* identified in the baseline urine culture at $\geq 10^5$ CFU/mL (or the same pathogen present concurrently in blood cultures and in urine).
  - No more than two microorganisms identified in the baseline urine culture, regardless of colony count.
- **Extended ME-TOC Population:** Patients who meet the definitions of both the Extended micro-ITT Population and CE-TOC Population. In addition, to be included in the ME-TOC Population, patients must not have a microbiological outcome of indeterminate at TOC.

4. STATISTICAL ANALYSES

4.1. General Considerations

EMB Statistical Solutions, LLC will generate the statistical analyses for the CSR in collaboration with Spero, including the associated datasets, detailed in this SAP. Programming of the datasets and the statistical analyses will be performed using SAS® software, Version 9.4 or later, unless otherwise specified (SAS Institute, Cary, NC 27513, USA). Programs will be validated prior to finalization as indicated in the Quality Control Plan (e.g., dataset creation and TLF programs will be validated with independent programming). In addition, all program outputs will be provided as portable document format (PDF) files and will be independently reviewed by a statistician. Upon completion of validation and quality review procedures, all programs and outputs will be retained.

Clinical Data Interchange Standards Consortium (CDISC) standards will be followed to facilitate potential electronic submission. All eCRF data and any externally provided data, such as laboratory data, will be retained in standard data tabulation model (SDTM) datasets. Plus, all data required for the planned analyses, including derived variables, will be provided in analysis data model (ADaM) data sets.

The SDTM and ADaM datasets will be provided as SAS® transport files. In addition, relevant study data from the eCRFs as well as derived variables will be provided in patient data listings. Data listings supplied as part of the CSR will be sorted by study site number concatenated with patient number, plus assessment dates or time points, if applicable.

4.1.1. Common Statistical Methods and Data Presentations

Unless otherwise specified, safety analyses will be based on the Safety Population. The population for each efficacy analysis will be specified in respective SAP sections. Summaries will include results for each treatment group separately.

All categorical data will be reported using the number of observations and percentages for each category. Presentation will be of the form XX (XX.X%), where the percentage is presented to one decimal in parentheses, except for one hundred percent which will be presented as 100%. In the case of a frequency of zero, the frequency and percentage will be presented as 0 rather than 0 (0%). Percentages will be based on non-missing data unless otherwise specified.

Summaries for continuous variables will include the number of observations, mean, standard deviation (SD), median, minimum, and maximum values. All mean and median values will be rounded to one more decimal place than the measured value. SD values will be rounded to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

Date variables will be formatted as DDMMMYYYY for presentation.

4.1.2. Missing Data, and Data Errors

Patients who receive study treatment other than the one to which they were randomized will be presented according to their randomized treatment in summaries based on randomized assignment and according to the treatment received in summaries based on the received treatment. Data listings will clearly denote whether randomized or actual treatment is being used. These patients will be noted in the CSR. Likewise, any other data errors identified in the final database will simply be noted in the CSR so long as the error does not impact the findings of the study.

For overall response, clinical response, and microbiological response, see Section 4.7.1, Section 4.8.1.1, and Section 4.8.1.2, respectively, for how response will be calculated for patients with missing data. In particular for analyses in the micro-ITT Population, unless otherwise classified as a failure, patients with missing data at a particular visit will be defined as indeterminate and will be included in the denominator for the calculation of response rate at that visit (thus considered to be failures). Inclusion in the CE (and thus ME) Population for a visit by definition requires an outcome assessed as clinical cure or clinical failure at that visit. The impact of missing data for the primary estimand-based analysis will be addressed through the sensitivity analysis detailed in Section 4.7.3. For the remaining endpoints, analyses will be based on the observed cases. All data summaries will identify the number of patients with data, so the number of patients with missing data for each variable can be deduced from the data summaries. Handling of other types of missing data, e.g., missing items scores in a validated instrument or missing attributes of an AE, like start date or relatedness, will be addressed in the respective sections of this SAP.

4.1.3. Coding of Adverse Events/Medical History and Prior/Concomitant Medications

AEs and medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0 or higher. Prior/concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODRUG/2006QA or newer

version). The specific versions of the dictionaries used for reporting will be specified in the Data Management Plan (DMP) and will be reported in the CSR.

4.1.4. Definition of Study Time Points

Baseline is defined as the most recent value prior to the start of treatment with IP or comparator and can be Screening or Day 1 with the exception of temperature.

Maximum daily temperature will be presented in the tables. Per the protocol, if the Screening visit and Day 1 occur on same calendar day, vital signs at Screening are required, while repeated Day 1 vital signs are optional. If repeated vital signs are collected, only the highest daily temperature is to be recorded in the eCRF. For these cases, the Baseline value will be defined as maximum temperature from pre-dose assessments, and the value for 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. Unscheduled assessments from central laboratory will be used to derive Baseline values (if occurred prior to first study treatment) and worst post-Baseline values for clinical laboratory and ECG assessments.

Out-of-window visits will affect evaluability in CE Populations. Protocol-defined timing of visits and windows are as follows:

- EOT: Occurs on the calendar day or the day following (+1 day) the last dose of study treatment
- TOC: Day 17 ±2 days
- LFU: Day 25 ±2 days

4.1.5. Microbiological Data Definitions

A Baseline urine pathogen is defined as a causative bacteria present at $\geq 10^5$ CFU/mL in a baseline urine culture with no more than two organisms isolated from the sample collected. A post-Baseline urine pathogen is defined as a causative bacteria present at $\geq 10^3$ CFU/mL in a post-baseline urine culture with no more than two organisms isolated from the sample collected.

A Baseline blood pathogen is defined as a noncontaminant bacteria identified in a blood culture obtained at Baseline. A post-Baseline blood pathogen is defined as a noncontaminant bacteria identified in a blood culture obtained at post-Baseline.

The term “uropathogen” refers to the urine pathogen and/or the blood pathogen that is the causative cUTI/AP pathogen. “Baseline pathogen” and “Baseline uropathogen” are used interchangeably.

The identification of pathogens and the assessment of microbiological response will always use the central laboratory results (i.e., identification) unless there are no data available from the central laboratory (e.g., an isolate was not received from the central laboratory, or the isolate was non-viable). If it is not possible to use central microbiology laboratory results, local microbiology laboratory results will be used.

Enterobacterales, *E. faecalis, S. aureus,* and *S. saprophyticus* will always be considered causative pathogens. Patients with these Enterobacterales uropathogen(s) and either co-infection with *E.*

faecalis, S. aureus, and *S. saprophyticus,* or no co-infecting causative pathogen will be eligible for inclusion into the micro-ITT Population and/or the GP Population. It will be necessary however, to identify co-infections with other causative pathogens to determine patients who are ineligible for the micro-ITT and/or GP Populations as outlined in Table 7. For details regarding which organisms will be classified as pathogens or non-pathogens see Appendix 3.

Table 7: Baseline Urine Culture Results and micro-ITT and Gram-positive Population Eligibility

Baseline Urine Culture Result		Include in micro-ITT Population?	Include in GP Population?
Bacteria #1	**Bacteria #2**		
Enterobacterales $\geq 10^5$ CFU/mL	N/A	Yes	No
E. faecalis, S. aureus, or *S. saprophyticus* $\geq 10^5$ CFU/mL	N/A	No	Yes
Enterobacterales $\geq 10^5$ CFU/mL	Enterobacterales $\geq 10^5$ CFU/mL	Yes	No
Enterobacterales $\geq 10^5$ CFU/mL	Either *E. faecalis,* or *S. aureus,* or *S. saprophyticus* $\geq 10^5$ CFU/mL	Yes	Yes
Enterobacterales $\geq 10^5$ CFU/mL	Any bacteria $< 10^5$ CFU/mL[1]	Yes	No
Enterobacterales $\geq 10^5$ CFU/mL	Species not considered to be causative of cUTI/AP $\geq 10^5$ CFU/mL (per Appendix 3)	Yes	No
Enterobacterales $\geq 10^5$ CFU/mL	Species other than Enterobacterales, *E. faecalis, S. aureus,* or *S. saprophyticus* considered to be causative of cUTI/AP $\geq 10^5$ CFU/mL (e.g., *Pseudomonas aeruginosa*; per Appendix 3)	No	No
E. faecalis, S. aureus, or *S. saprophyticus* $\geq 10^5$ CFU/mL	*E. faecalis, S. aureus,* or *S. saprophyticus* $\geq 10^5$ CFU/mL	No	Yes
E. faecalis, S. aureus, or *S. saprophyticus* $\geq 10^5$ CFU/mL	Any bacteria $< 10^5$ CFU/mL[2]	No	Yes
E. faecalis, S. aureus, or *S. saprophyticus* $\geq 10^5$ CFU/mL	Species not considered to be causative of cUTI/AP $\geq 10^5$ CFU/mL (per Appendix 3)	No	Yes
E. faecalis, S. aureus, or *S. saprophyticus* $\geq 10^5$ CFU/mL	Species other than Enterobacterales, *E. faecalis, S. aureus,* or *S. saprophyticus* considered to be causative of cUTI/AP $\geq 10^5$ CFU/mL (per Appendix 3)	No	No

AP, acute pyelonephritis; CFU, colony forming unit; cUTI, complicated urinary tract infection; GP, Gram-positive; micro-ITT, microbiological Intent-to-Treat; mL, milliliter.

[1] *Exception*: If a species considered to be causative of cUTI/AP (other than another Enterobacterales or *E. faecalis, S. aureus*, or *S. saprophyticus)* is identified in urine $< 10^5$ CFU/mL, and the same species is also found in blood, the patient would be excluded from the micro-ITT Population. If *E. faecalis, S. aureus*, or *S. saprophyticus* is identified

in urine <10^5 CFU/mL and the same species is also found in blood, the patient would be included in the micro-ITT and GP Populations.
[2] *Exception*: If a species considered to be causative of cUTI/AP other than Enterobacterales is identified in urine <10^5 CFU/mL and the same species is also found in blood, the patient would be included in the micro-ITT Population. If a species considered to be causative of cUTI/AP (other than *E. faecalis, S. aureus*, or *S. saprophyticus)* is identified in urine <10^5 CFU/mL and the same species is also found in blood, the patient would be excluded from the GP Population.

If more than one uropathogen of the same species is isolated in a patient (e.g., urine and blood or two urine isolates), the isolate with the highest MIC to study drug received using CLSI criteria will be selected, and all susceptibility data (MICs, zone sizes) associated with that particular isolate will be used in summaries.

Target antibiotic-resistant phenotypes of interest for Enterobacterales isolates will be identified based on the susceptibility criteria outlined in Table 8.

Table 8: Resistant Pathogen Phenotypes for Enterobacterales Isolates

Phenotype	Criteria (CLSI-2023 M-100 Ed33E)	Comment
ESBL-phenotype	*Escherichia coli, Klebsiella pneumoniae*, and *Klebsiella oxytoca* isolates with MIC ≥8 µg/mL for cefpodoxime or MICs ≥2 µg/mL for ceftazidime, aztreonam, cefotaxime, or ceftriaxone. *Proteus mirabilis* with MICs ≥2 µg/mL for cefpodoxime, ceftazidime, or cefotaxime. For all other Enterobacterales, isolates with ceftazidime and/or ceftriaxone MICs ≥2 µg/mL will be submitted for molecular analysis to identify β-lactamase genes	Criteria for selecting isolates for molecular characterization of β-lactamase genes
FQ-NS	Levofloxacin MIC ≥1 µg/mL	CLSI breakpoint for intermediate and resistant susceptibility
TMP-SMX-R*	TMP-SMX MIC ≥4 µg/mL	CLSI breakpoint for resistance
MDR	Non-susceptibility (i.e., resistant or intermediate) to at least one agent in at least three antimicrobial classes	Antimicrobial classes include **Extended cephalosporins** (Ceftazidime, ceftriaxone, cefotaxime, cefpodoxime) and aztreonam, **Narrow spectrum cephalosporins** (Cefuroxime), **Carbapenems** (Imipenem, meropenem, ertapenem), **β-Lactam/β-Lactamase** Inhibitors (Piperacillin/tazobactam), **Aminoglycosides** (Gentamicin), **Fluoroquinolones** (Levofloxacin), **Tetracyclines** (Tetracycline), **Sulphonamides** (Trimethoprim-sulfamethoxazole)

CLSI, Clinical and Laboratory Standards Institute; ESBL, extended spectrum ß-lactamase; NS, nonsusceptible, based on CLSI guidelines, antibiotics with a designated susceptible breakpoint only are reported as not susceptible; FQ-NS, fluoroquinolone-not susceptible; MIC, minimum inhibitory concentration; mL, milliliter; TMP-SMX-R, trimethoprim-sulfamethoxazole-resistant; MDR, multi-drug resistant, NS (intermediate and resistant) to ≥3 drug classes.
*TMP-SMX is tested in the ratio 1:19.

4.2. Patient Disposition

The number and percentage of patients in each analysis population along with reasons for exclusion from each population will be provided by treatment group and overall.

The number and percentage of patients randomized will be presented by treatment group and overall, and generated by region and country and also by site. Regions will include the following:

- Central and Eastern Europe (Bosnia and Herzegovina, Bulgaria, Croatia, Estonia, Georgia, Hungary, Latvia, Macedonia, Poland, Republic of Moldova, Romania, Serbia, and Slovakia)
- North America (United States)
- South America (Argentina and Brazil)
- Other (Greece, India, South Africa, and Turkey)

Patients who received treatment with IP or comparator, completed the study and/or treatment as recorded in the eCRF, discontinued prematurely from the study and/or treatment, along with the reason for discontinuation as recorded in the eCRF, will be summarized with number and percentage for all patients in the ITT, Safety, and micro-ITT Populations, by treatment group and overall.

Listings will be provided to support the above disposition summaries for the ITT Population.

4.3. Protocol Deviations

Protocol deviations will be tabulated in the ITT and micro-ITT Populations by treatment group and overall. The summary will include number and percentage of patients with at least one major deviation, at least one minor deviation, and at least one occurrence in each deviation category, as well as the deviations that resulted in exclusion from the CE Population.

A supporting listing of all protocol deviations (including categorization) will be provided for the ITT Population.

4.4. Baseline Characteristics and Patient History

4.4.1. Demographics and Baseline Characteristics

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

Demographics and Baseline characteristics will be summarized by treatment group and overall to include age (in years) and age category at time of informed consent as recorded in the eCRF (≥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 / Multiple), ethnicity (Hispanic or Latino / Not Hispanic or Latino / Not Reported), site region (Central/Eastern Europe, North America, South America, and Other), and body mass index (BMI) at screening (kilogram [kg]/meter [m]^2).

Baseline clinical characteristics will be summarized by treatment group and overall to include baseline diagnosis (AP vs. cUTI), urinary tract instrumentation at Baseline (Yes/No), estimated

creatinine clearance (CrCl) in mL/min, CrCl categories (≤30, >30 to ≤50, >50 mL/min), bacteremia at Baseline, receipt of prior systemic antibiotics, and modified systemic inflammatory response syndrome (SIRS) criteria.

Note the CrCl summary will use the central lab value if available, or if missing then the electronic data capture system calculated local lab value, based on the Cockcroft-Gault formula (Cockcroft 1976).

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 in the eCRF 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 in the eCRF is considered to have cUTI without AP (i.e., complicated cystitis).

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

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

Listings will be provided for all demographic and Baseline characteristics for the ITT Population.

4.4.2. Medical/Surgical History and Current Medical Conditions

Medical and surgical history (including urological history and any active/inactive conditions diagnosed within the previous 5 years) will be summarized by System Organ Class (SOC) and preferred term (PT), showing the number and percentage of patients having at least one occurrence of a condition. Summaries will be presented by treatment group and overall, for the Safety and micro-ITT Populations.

Baseline urinary tract signs and symptoms (term and severity) will be summarized by treatment group and overall for the Safety and micro-ITT Populations.

Supportive listings will be provided for the ITT Population.

4.4.3. Baseline Pathogens

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. Select summaries will also be presented in the GP Population.

Baseline pathogens (i.e., pathogens isolated at ≥10^5 CFU/mL from baseline urine cultures and blood pathogens identified concurrently in urine) will be presented by genus and species and

summarized by treatment group. Baseline pathogen summaries will be presented separately for bacteremic patients overall, bacteremic patients with the same species identified at $\geq 10^5$ CFU/mL in the urine, and bacteremic patients with the same species identified at $<10^5$ CFU/mL in the urine.

The number of patients with Baseline Enterobacterales uropathogens will be presented, as well as the number of patients with Gram-positive vs. Gram-negative uropathogens, and the number of patients with monomicrobial vs. polymicrobial (including patients with two Enterobacterales, two Gram-positive pathogens, and one Enterobacterales and one Gram-positive pathogen) infection.

In vitro testing results of Baseline pathogen susceptibility to tebipenem, ceftazidime, levofloxacin, and trimethoprim/sulfamethoxazole will be separately summarized for all Baseline pathogens isolated from urine and/or blood by treatment group and overall for the above populations. For ceftazidime and levofloxacin, results will be presented as "susceptible" and "not susceptible" (including subsets of "intermediate" and "resistant"); for trimethoprim/sulfamethoxazole, results will be presented as "susceptible" and "resistant").

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

- **Per-pathogen** summary tables will present the total number of Baseline pathogens of each phenotype presented by genus and species. ESBL, FQ, TMP-SMX, and MDR categories are not mutually exclusive (e.g., a pathogen that is ESBL-phenotype but FQ-susceptible [FQ-S] should still be counted in both summary rows).
- **Per-patient** summary tables will present the total number patients with at least one Baseline pathogen in each phenotype category. For patients with two Baseline pathogens of different species, if one pathogen meets criteria for a resistance phenotype, the patient will be counted in that phenotypic category.

The distribution of Baseline pathogen MIC to study drugs and/or those outlined for resistance selection (see Table 8) will be presented by treatment group and overall for each pathogen/pathogen category. The following summaries will be performed:

- Distribution of tebipenem, imipenem, ceftazidime, levofloxacin, and trimethoprim-sulfamethoxazole MIC of Baseline Enterobacterales
- Distribution of tebipenem and imipenem MICs of *E. faecalis*, *S. aureus*, and *S. saprophyticus*
- Distribution of tebipenem and imipenem MICs of Enterobacterales by resistance phenotype:
  - ESBL-phenotype
  - FQ-NS
  - TMP-SMX-R
  - MDR

MIC values will be reported by the central laboratory. To determine cumulative MIC percentages programmatically, MIC values first 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 then will be determined from lowest to highest value, i.e., 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.

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.

Molecular testing performed results will be summarized in an addendum to the CSR. Molecular characterization of clinical isolates will include identification of β-lactamase genes among isolates that meet the pre-specified ESBL screening criteria. In addition, isolates from the same species recovered from the same patient during the Baseline and follow-up visits will be subjected to multi-locus sequence typing (MLST).

Urine and blood culture results and susceptibility testing results for each isolate tested will be listed by patient and treatment group for the ITT Population (patients included into the micro-ITT Population and/or GP Population will be flagged).

4.5. Prior and Concomitant Medications

Any patient record of prior treatment must be documented in the appropriate eCRF page. Concomitant therapy taken between the dates of the first dose of study treatment and the last study visit, inclusive, are to be listed in the appropriate eCRF page.

For reporting purposes, a medication will be considered prior if administered within 30 days of the date of first dose of IP or comparator. A concomitant medication is defined as any medication taken during the period from the date of first dose of IP or comparator through the late follow-up visit. A medication that was started before the date of first IP or comparator dose and continues after the first dose will be included as both a prior and concomitant medication.

In order to simplify the process of differentiation between the prior and concomitant medications, 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 at discharge from the study.

If start date is completely missing but end date is before the first dose of study treatment, start date will not be imputed, and the medication will be considered prior. If start date is completely

missing but end date is after the first dose of study treatment or if both start and end dates are completely missing, they will not be imputed, and medication will be considered as both prior and concomitant.

Prior antibiotics and concomitant (both antibiotic and non-antibiotic) medications will be summarized by the Anatomical Therapeutic Chemical (ATC) class (ATC Level 2 and ATC Level 4) and preferred drug name. Antibiotic and non-antibiotic treatments will be summarized separately. Patients with 1 dose vs. >1 dose of prior antibiotics will be presented. The summary for concomitant antibiotics treatment will be further split as follows: any concomitant antibiotic, concomitant antibiotics to treat cUTI/AP, and concomitant antibiotics to treat any other infection. Summaries will be presented by treatment group and overall, for the Safety and micro-ITT Populations. The number and percent of patients who received each medication will be presented.

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

4.6. Study Treatment Exposure

The following parameters will be calculated for the IP and comparator exposure data:

- Actual total IV dose (mg) received throughout the study, defined as the sum of all IV doses received by the patient
- Actual total oral dose received throughout the study (mg), defined as the sum of all 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 doses taken/planned number of doses. Compliance with IV drug will be defined in a similar way.

The above-defined parameters will be summarized in the Safety Population by treatment group. Duration of the IV and oral treatment will be summarized both categorically (1 day, 2 days, etc.) and as a continuous variable. Compliance will be summarized both categorically (≥80%, <80%) and as a continuous variable.

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

4.7. Primary Efficacy Estimand Analysis

The primary treatment effect to be estimated (estimand) is overall response (combined per-patient clinical cure plus favorable microbiological response) at the TOC visit in the micro-ITT Population. The primary treatment effect will be estimated regardless of treatment discontinuation, as per the treatment policy strategy. The ICE of use of non-study potentially effective systemic antibacterial therapy for the treatment of the index infection (cUTI/AP) is captured through the definitions of microbiological and clinical response and will be counted as

failures (composite strategy). If a patient experiences both ICEs of study treatment discontinuation and use of potentially effective systemic antibacterials, then a composite strategy (assigning overall response as a failure) will be used from the point that the relevant systemic antibacterial was taken. Further details on the primary estimand are provided in Section 1.1.1.

4.7.1. Definition of Endpoint

Overall response (combined per-patient clinical cure plus favorable microbiological response) at TOC in the micro-ITT Population is the primary endpoint. See Section 1.1.1 for the definition of clinical cure and favorable microbiological response.

See Section 4.8.1.1 and Section 4.8.1.2 for further details on the components of clinical response and microbiological response, respectively. In particular, patients who require non-study antibacterial therapy for treatment of the index infection or with death prior to the TOC assessment will be assessed as clinical failure. Patients with missing data at TOC, or who are lost to follow-up, will be defined as indeterminate for the primary analysis and will be included in the denominator for the calculation of overall response rate. Thus, patients with an indeterminate outcome will be considered failures for the primary analysis.

For overall response at TOC, patients will be categorized as:

- Responder: clinical cure plus microbiological eradication
- Non-responder: clinical cure only, microbiological eradication only, or neither
- Indeterminate response: indeterminate clinical response, indeterminate microbiological response, or both

Table 9 provides a summary of the overall response determination at TOC.

Table 9: Summary of Overall (Combined) Response at TOC

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

TOC, Test-of-Cure.

4.7.2. Main Analytical Approach

See Section 2.1 for the statistical hypotheses and testing for the primary estimand.

The number and percentage of patients in each overall response category (responder and non-responder [including indeterminate]) at TOC will be reported by treatment group, as well as the treatment difference in responder rates and the associated 95% CI. The 95% CI will be calculated using the method of Miettinen and Nurminen stratified as indicated in Section 2.1.

In the event that any patients are mis-stratified, the actual baseline diagnosis, age at informed consent, and urinary tract instrumentation at Baseline collected in the eCRF will be used to create an actual pooled stratification and used for analysis rather than strata as randomized.

4.7.3. Sensitivity Analyses

Sensitivity analyses will be performed to investigate the robustness of the primary efficacy results for the primary estimand. The following sensitivity analyses will be performed in the micro-ITT Population:

1. An analysis of overall response at TOC will be performed unadjusted for the stratification factors.
2. If any patients are mis-stratified, an analysis of overall response at TOC will be conducted using the pooled stratification as randomized (instead of the actual stratum as collected in the eCRF).
3. To assess the impact of missing data on overall response at TOC in the micro-ITT Population, a multiple imputation (MI) method will be used with a missing at random assumption. Missing data is defined as a subject not having a clinical response and/or microbiological response at TOC (i.e., has indeterminate response). Patients classified as failures at TOC (i.e., non-responders) without missing data will still be considered failures and will not require imputation. The missing data of overall (combined) response at TOC will be imputed. The MI procedure of the SAS® system will be used to generate 1000 sets of data with missing values for clinical response and microbiological response imputed from observed data. The seed number to be used will be 503785. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo method of the MI procedure. If the pattern of missing data is not monotonic, then the fully conditional specification method of the MI procedure will be used. A discriminant function will be employed to model the missing clinical and microbiological response values, with the following covariates included in the imputation model: age at time of consent (≥18 to <65 years vs. ≥65 years), baseline diagnosis (cUTI vs. AP), presence or absence of urinary tract instrumentation at Baseline, clinical response at the EOT visit (for clinical response only), microbiological response at the EOT visit (for microbiological response only), site region (for clinical response only), and randomized treatment. Any patients who have a missing value for one or more of the covariates will be excluded from the relevant imputation model.

   For each of the 1000 datasets, overall response at TOC then will be derived per Section 4.7.1. The imputed datasets will be analyzed using the methodology described for the primary analysis in Section 4.7.2. The results from the analysis of the multiple imputed datasets will be combined by the MIANALYZE procedure of the SAS® system.
4. Repeat the primary analysis based on observed data only. This would exclude subjects with missing (i.e., indeterminate) overall (combined) response at TOC.

4.7.4. Supplementary Analyses

The primary efficacy analysis will be performed for the ME-TOC and GP Populations to assess general consistency with the primary analysis.

Another supplementary analysis of the primary endpoint at TOC in the micro-ITT Population will be performed where patients who are clinical cure, but got additional antibacterial treatment

with the potential to treat the Baseline pathogen for reasons other than cUTI/AP (i.e., a remote infection) will be classified as an indeterminate instead.

For overall response at TOC, reasons for non-responder (clinical failure only, microbiological persistence only, clinical failure and microbiological persistence) and reasons for indeterminate (indeterminate clinical response only, indeterminate microbiological response only, indeterminate clinical and microbiological response) will be summarized in the micro-ITT Population using numbers and percentages of patients.

The primary efficacy data will be listed for the ITT Population, with a flag to denote patients included in the micro-ITT, Extended micro-ITT, and GP populations.

4.7.5. Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint in the micro-ITT Population will be conducted. Descriptive statistics along with treatment difference and associated 95% CI (calculated using the unstratified method of Miettinen and Nurminen) will be presented in tables as well as in forest plots for the following subgroups using Baseline data:

- Baseline diagnosis (AP, cUTI, cUTI with and without AP)
- Age category (≥18 to <65 years, ≥65 to <75, ≥75 years)
- Urinary tract instrumentation at Baseline (Yes, No)
- Sex (Male, Female)
- Race (Asian, Black or African American, White, Other*)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Site region (Central/Eastern Europe, North America, South America, and Other)
- Creatinine clearance category (≤30, >30 to ≤ 50, >50 mL/min)
- Bacteremia at Baseline (Yes, No)
- Modified SIRS at Baseline (Yes, No)**
- Receipt of prior systemic antibiotics (Yes, No)
- Monomicrobial vs Polymicrobial Infection
- Gram-positive Baseline pathogen (Yes, No)
- Baseline pathogen (genus, species; also tebipenem MIC and imipenem MIC)
- Baseline pathogen resistance category (based on the susceptibility of the pathogens isolated from urine and/or blood at Baseline and criteria outlined in Table 8):
  - ESBL-phenotype Baseline pathogens
  - FQ-NS Baseline pathogens
  - TMP-SMX-R Baseline pathogens
  - MDR Baseline pathogen

* Includes 'Other', 'Not Reported', 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' race categories and patients with more than one race selected on the eCRF 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 4.4.1).

Overall response at TOC will also be summarized by tebipenem MICs for Baseline pathogens isolated from urine and/or blood in the micro-ITT and Extended micro-ITT Populations.

4.8. Secondary Efficacy Estimands Analysis

For each of the secondary efficacy endpoints the estimand will follow a similar approach to the estimand for the primary efficacy endpoint and will use the same general strategies for the ICEs. See Sections 1.1.2 and Appendix 1for further details.

4.8.1. Definition of Endpoints

4.8.1.1. Clinical Response

Clinical Response at EOT and TOC

Clinical response at EOT and TOC are defined based on assessment by the Investigator of change in Baseline signs and symptoms of cUTI/AP as follows:

- 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: symptoms of cUTI or AP present at study entry have not completely resolved, or new symptoms have developed and require the initiation of a non-study antibacterial drug therapy, or death
- Clinical indeterminate: insufficient data are available to determine if the patient is a cure or failure (e.g., patient is lost to follow-up or has missing data at the respective visit).

Note: If a patient is assessed as a clinical failure at EOT or TOC, the patient is automatically considered a failure at subsequent visits. Otherwise, clinical response will be programmatically derived as indeterminate if clinical response is missing due to missed visit.

Clinical Response at LFU

Clinical response at LFU is also defined based on assessment by the Investigator of change in Baseline signs and symptoms of cUTI/AP as follows:

- Cure, including sustained clinical cure: sustained clinical cure is defined as met criteria for clinical cure at TOC, and remained free of new or recurrent signs and symptoms of cUTI or AP at the LFU visit such that no further antibacterial therapy is warranted

- Failure, including clinical relapse: clinical relapse is defined as met criteria for clinical cure at TOC, but new signs and symptoms of cUTI or AP are present at the LFU visit, and the patient requires antibiotic therapy for the cUTI
- Clinical indeterminate: Insufficient data are available to determine if the patient is a sustained clinical cure or clinical relapse.

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

4.8.1.2. Microbiological Response

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

Per-pathogen Microbiological Response

The per-pathogen microbiological response at [redacted], EOT, TOC, and LFU will be determined programmatically based on the definitions below. [redacted].

- Microbiologic eradication: The Baseline pathogen is 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 the Baseline pathogen identified at study entry. Pathogens with an outcome of microbiologic persistence at EOT will be considered persistent at TOC and LFU. Pathogens with an outcome of persistence at TOC will be considered persistent at LFU
  - Persistence with increasing MIC: Pathogen response is persistence at TOC or LFU and post-baseline urine and/or blood isolate displays ≥4-fold higher MIC to study therapy received compared to the MIC of Baseline pathogen
- Microbiologic indeterminate: No follow-up urine culture is available, or urine cultures are missing, or the follow-up urine culture cannot be interpreted for any reason, or the follow-up urine culture is considered contaminated.

Note: Post-Baseline blood cultures are to be taken only if positive at Baseline or as clinically indicated. If follow-up blood cultures are missing in a patient who was bacteremic at Baseline, and the Baseline pathogen is $<10^3$ CFU/mL in urine culture, the microbiological response will be presumed based on the clinical outcome of the patient (i.e., the pathogen will be considered eradicated if the patient is a clinical cure and persistent if the patient is a clinical failure).

Per-patient Microbiological Response

An overall per-patient microbiological response will be programmatically derived at [redacted] EOT, TOC, and LFU based on the per-pathogen microbiological responses noted above. For

patients with monomicrobial infection, the per-patient microbiological outcome will be identical to the per-pathogen outcome for their Baseline pathogen. For patients with polymicrobial infections, both Baseline pathogens must be eradicated to have a per-patient outcome of eradication. If at least one Baseline pathogen has microbiological response of persistence, a per-patient microbiological response will be assigned as persistence. [redacted]

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

- Microbiologic eradication: Patient 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; patients with a microbiologic persistence outcome at EOT will be considered a persistence at TOC
- Microbiologic indeterminate: No follow-up urine culture is available, or urine cultures are missing, or the follow-up urine culture cannot be interpreted for any reason

Per-patient 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:

- Eradication, including sustained microbiologic eradication: Sustained microbiologic eradication is defined as microbiologic eradication at TOC and no subsequent urine culture after TOC demonstrating recurrence of the original Baseline uropathogen at $\geq 10^3$ CFU/mL
- Persistence, including microbiologic recurrence: Microbiologic recurrence is defined as: 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 urine culture results are missing, or the follow-up urine culture cannot be interpreted for any reason.

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

4.8.1.3. Overall Response

Overall response at the EOT and LFU visits will be defined similarly to the primary endpoint at the TOC visit, incorporating the applicable clinical and microbiological success response definitions for each visit.

4.8.2. Main Analytical Approach

Overall response at EOT and LFU in the micro-ITT Population and overall response at EOT, TOC, and LFU in the ME Population will be summarized with number and percentage of patients. Treatment difference in responder rates between the two treatment groups and the associated 95% CI will be calculated using the same approach as the primary endpoint.

Note that references to analyses in the ME and CE Populations means the ME and CE Populations for the applicable visit will be used (e.g., ME-EOT, ME-TOC, ME-LFU, etc.).

Clinical response at EOT, TOC, and LFU will be summarized with number and percentage of patients in the micro-ITT, CE, and ME Populations. At the LFU visit, "Failure at TOC Carried Forward" and "Clinical Relapse" subcategories of "Failure, Including Clinical Relapse" will be summarized. Treatment difference in cure rates between the two treatment groups and the associated 95% CI will be calculated using the same approach as the primary endpoint.

Per-patient microbiological response at EOT, TOC, and LFU will be summarized with number and percentage of patients in the micro-ITT and ME Populations. Treatment difference in favorable response rates between the two treatment groups and the associated 95% CI will be calculated using the same approach as the primary endpoint.

Per-pathogen microbiological response at EOT, TOC, and LFU will be summarized by pathogen counts and percentages in the micro-ITT and ME Populations. The summaries will be generated separately for Baseline pathogens isolated from urine and/or blood and for Baseline pathogens isolated from blood only.

Overall, clinical, and per-patient microbiological response at EOT, TOC, and LFU in patients with Baseline drug-resistant Enterobacterales (as outlined in Table 8, phenotype categorization for a patient will be determined based on Baseline pathogens isolated from urine and/or blood) will be summarized with number and percentage of patients in the micro-ITT and ME Populations. Treatment difference in success rates between the two treatment groups and the associated 95% CI will be calculated using the same approach as the primary endpoint. 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.

4.8.3. Supplementary Analyses

Secondary endpoints for overall response, clinical response, and microbiological response will also be summarized in the GP Population.

The secondary efficacy data will be listed for the ITT Population, with a flag to denote patients included in the micro-ITT, Extended micro-ITT, and GP populations.

4.8.4. Subgroup Analyses

Overall response, clinical response, and per-patient microbiological response by visit will be summarized for patients with a baseline diagnosis of AP vs. cUTI in the micro-ITT Population.

Clinical response and per-patient microbiological response by visit will be summarized for patients with bacteremia at Baseline in the micro-ITT and ME Populations.

Clinical cure at EOT, TOC, and LFU will be summarized by Baseline pathogen in the micro-ITT and ME Populations. The summaries will be generated separately for Baseline pathogens isolated from urine and/or blood and for Baseline pathogens isolated from blood.

Per-pathogen microbiological response at EOT, TOC, and LFU will be summarized by Baseline pathogens and by resistant Baseline pathogen phenotypes (as outlined in Table 8, 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. The summaries will be generated separately for Baseline pathogens isolated from urine and/or blood and for Baseline pathogens isolated from blood.

In addition, clinical response and per-pathogen microbiological response at TOC will be summarized by tebipenem MIC for the TBP-PI-HBr treatment group, and by imipenem MIC for the imipenem-cilastatin treatment group, for the micro-ITT Population. A similar summary will be performed for each subset of Baseline resistant pathogens (as outlined in Table 8).

Clinical response and per-pathogen microbiological response at TOC will also be summarized by tebipenem MICs for Baseline pathogens isolated from urine and/or blood in the micro-ITT and Extended micro-ITT Population (TBP-PI-HBr treatment group).

[redacted]

4.9.2. Main Analytical Approach

[redacted]. 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.

[redacted]

For a subset of Gram-negative pathogens meeting phenotypic CLSI ESBL 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. Per-patient and per-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.

An additional analysis will be performed in which persistent outcomes will be reclassified as eradicated if MLST indicates that the follow-up species is not clonally related to Baseline pathogen. Overall response and per-patient microbiologic response summaries will be produced for the micro-ITT Population and reported in an addendum to CSR.

[redacted].

4.10. Safety Analyses

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

Primary assessments of safety will include assessments of treatment-emergent adverse events (TEAEs), clinical laboratory (hematology, clinical chemistry, coagulation, and urinalysis) changes, vital sign changes, and electrocardiograms (ECGs).

4.10.1. Adverse Events

TEAEs are defined as events that are newly occurring or worsening from the time of the first dose of IP or comparator through LFU. Since AEs are to be recorded from the first study treatment dosing through LFU per the protocol, all AEs for the study (when collected as intended) will be considered TEAEs.

The Principal Investigator (PI) is obligated to assess the relationship between the study treatment and each AE occurrence using the categories of unrelated, unlikely, possible, and probable. An AE will be considered related to study treatment for summary if the PI-assessed causality is possibly related, probably related, or missing.

In addition, the PI will assess the intensity of each AE using the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grades: Mild (Grade 1), Moderate (Grade 2), Severe (Grade 3), Life-Threatening or Disabling (Grade 4), and Death (Grade 5). Events with unrecorded intensity will be considered Severe (Grade 3) for statistical summaries. Any preferred terms with a missing intensity will be described in the table footnotes.

A serious AE (SAE) is any AE occurring at any dose and regardless of causality that met one or more of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of an existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically important event or reaction

In this study, progression or worsening of the index infection (cUTI/AP) is captured as an efficacy outcome (clinical failure) rather than as an AE. However, if clinical failure or complications of the index cUTI/AP meets any of the above seriousness criteria, the event will be reported as an SAE.

Wherever possible, imputation rules will be used to classify AEs with missing dates as treatment-emergent. 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 study 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 study treatment start, then the study 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 study treatment start, then use January 01. If the year matches the year of study treatment start, then use the study 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 the AE is listed as ongoing.

If either AE start or end date is completely missing, they will not be imputed, and the AEs with completely missing start date will be considered treatment-emergent.

4.10.1.1. Treatment-Emergent Adverse Events

An overall summary of TEAEs will be presented, which will include the number and percentage of patients with at least one TEAE, serious TEAE, TEAE related to study treatment, serious TEAE related to study treatment, TEAE with severe or greater intensity, TEAE leading to premature discontinuation of study treatment, TEAE leading to early withdrawal from study, and TEAE leading to death, along with the total number of events.

The number of patients with at least one event, associated percentage, and number of events for TEAEs, serious TEAEs, TEAEs related to study treatment, serious TEAEs related to study treatment, TEAEs leading to premature discontinuation of study treatment, TEAEs leading to the early withdrawal from study, and TEAEs leading to death will be presented by system organ class (SOC) and preferred term (PT), by treatment group and overall. The summaries will display the SOC in alphabetical order, while PTs within the SOC will be presented in order of decreasing frequency of occurrence in the overall column.

A summary of TEAEs by maximum CTCAE intensity grade also will be displayed by SOC and PT, by treatment group and overall.

Summaries of TEAEs and serious TEAEs sorted by decreasing frequency of PT for TBP-PI-HBr then for imipenem-cilastatin will also be provided by treatment group and overall.

A patient with multiple TEAEs (different PTs) coded to the same SOC will be counted only once for that SOC, but will be counted each time for the different PTs within that SOC. A patient with separate events of the same PT (different start/stop dates) will be counted only once in the frequency tables for that PT. For the summaries by intensity grade or causality, a patient will be counted once for each TEAE at the highest intensity and strongest relationship to study treatment, respectively.

TEAE summaries will be repeated summarizing events which occurred starting from the first dose of study treatment through the EOT visit.

Listings will be provided for all TEAEs, serious TEAEs, TEAEs related to study treatment, serious TEAEs related to study treatment, TEAEs leading to premature discontinuation of study treatment, TEAEs leading to early withdrawal from the study, and TEAEs leading to death for the Safety Population.

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

4.10.1.2. Treatment-Emergent Adverse Events of Special Interest

TEAEs of special interest will be defined as possibly related to any of the following six topics of medically important AEs and have been identified through a search of preferred terms:

- TEAEs possibly indicative of Liver Disorders
- TEAEs indicating Diarrhea
- TEAEs indicating Hypersensitivity
- TEAEs indicating Hematological Disorders
- TEAEs indicating Renal Disorders

- TEAEs indicating Seizure

The six topics of special interest represented above were chosen based on the known class-effect safety topics for other carbapenem antibiotics and/or the β-lactam class (e.g., hypersensitivity, hematologic disorders representing low blood counts, etc.), or based on safety topics that are known to result in severe complications for any drug (e.g., liver disorders and/or drug-induced liver injury). The strategy or method that was used to identify these six topics is described in Appendix 4 and the predefined list of preferred terms to be used to search for TEAEs of special interest in this study is provided in Appendix 5.

The number and percentage of patients who experienced at least one event within each TEAE of special interest topic will be tabulated.

The incidence of TEAEs will also be summarized by SOC and PT within each TEAE of special interest topic. A supporting listing will be provided.

4.10.2. Clinical Laboratory Evaluations

The central safety laboratory will perform evaluations on blood and urine samples from the Screening, Day 1, Day 3, Day 5, Day 7, Day 9 (if still receiving study treatment), EOT, TOC, and LFU visits. Protocol Section 7.2.3.5 indicates the following analytes will be measured:

- hematology (hemoglobin, hematocrit, red blood cell [RBC] indices)
- thrombocyte count (platelets)
- reticulocyte count
- WBC count with differential (including neutrophils, eosinophils, basophils, lymphocytes and monocytes)
- coagulation (prothrombin time, international normalized ratio, activated partial thromboplastin time)
- blood chemistry:
  - electrolytes (sodium, potassium, chloride, bicarbonate)
  - non-fasting glucose
  - blood urea nitrogen (BUN)
  - creatinine (Cr) (including calculated CrCl using Cockcroft-Gault formula)
  - l-carnitine
- creatine kinase
- urate
- phosphate
- total calcium (corrected calcium will be derived separately for summary as:

  total calcium + 0.02 * [40 - albumin])
- cholesterol

- albumin
- total protein
- total bilirubin
- conjugated bilirubin
- gamma-glutamyl transferase
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- alkaline phosphatase (ALP)
- lactate dehydrogenase
- triglycerides
- complete urinalysis (pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, and leukocytes).

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

Reference ranges supplied by the laboratory will be 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.

All scheduled central clinical laboratory tests will be summarized by treatment group and overall using descriptive statistics for the actual value at each visit. In addition, change from Baseline will be summarized by visit for each quantitative parameter.

Shift tables of the worst post-Baseline laboratory toxicity based on CTCAE Version 5.0 grading relative to Baseline will be presented by treatment group for scheduled clinical laboratory tests with grading criteria available for programmatic determination. The number of patients in a particular treatment arm having both Baseline and post-Baseline results available for a test will be used as the denominator.

Additional presentations of laboratory parameters (chemistry and hematology parameters will be summarized separately) will include frequencies for worst post-Baseline values as follows:

- Patients with at least a 2-grade worsening from Baseline in CTCAE toxicity grade for any parameters
- Patients with post-Baseline CTCAE toxicity grade 4 and worse than Baseline for any parameters

Analysis of patients with post-Baseline aminotransferase and total bilirubin elevations by category will be done for worst post-Baseline values 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., a patient with an ALT value of 6x ULN will be presented under both >3x ULN and >5x ULN).

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 >3x ULN that is associated with both an ALP <2x ULN and an increase in bilirubin >2x ULN.

All laboratory data will be listed for 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).

Box plots of key central laboratory values (including ALT, AST, total bilirubin, gamma-glutamyl transferase, l-carnitine, BUN, Cr, corrected calcium, hematocrit, platelets, WBC, hemoglobin, basophils, eosinophils, lymphocytes, monocytes, and neutrophils) vs. visit will also be provided by treatment group.

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

4.10.3. Vital Signs

Vital sign assessments include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), respiratory rate (breaths per minute), and maximum daily temperature (° C). In cases where temperature has been measured multiple times in a single day, maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be collected at Screening, daily Day 1 through EOT (prior to daily IV infusions for imipenem-cilastatin or placebo-IV treated patients), TOC, and LFU. Any changes from Baseline vital signs deemed clinically significant in the opinion of the Investigator will be recorded as an AE.

Summary of vital sign observed values and changes from Baseline to scheduled post-Baseline visits will be presented by treatment group and overall.

A listing of vital signs data and of maximum daily temperatures will be presented for the Safety Population.

4.10.4. Electrocardiograms

A single 12-lead ECG will be performed at Screening, Day 1 (after the first dose of oral dose administration), and at the EOT visit (after the last dose of oral dose administration) 1 h (±15 min) and as otherwise clinically indicated after oral dose administration. Electrocardiogram parameters include heart rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec), RR interval (msec), QTcF interval (msec, calculated per Fridericia's formula).

Summary of ECG observed values and changes from Baseline to scheduled post-Baseline visits will be presented by treatment group and overall.

ECGs will be categorized as 'normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant' by the investigator and summarized by treatment group and overall for each visit.

Worst post-Baseline categorized QTcF values will be presented as follows:

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

A listing of ECG data will be presented for the Safety Population.

4.10.5. Other Safety Endpoints

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 but will be listed.

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

4.11. Pharmacokinetic Analyses

PK sampling will occur as indicated in schedule of assessments (see Appendix 2).

TBP plasma concentration-time data from TBP-PI-HBr treated patients will be used to characterize the PK of TBP in the target population using PK modeling, to be described in a separate PK Analysis Plan. Concentration values will be listed in the CSR by patient and actual time after dose.

[redacted]

4.12. Changes to Protocol-Planned Analyses

There are no changes to the analyses described in the protocol.

5. REFERENCES

Clinical and Laboratory Standards Institute (CLSI) (2023). Performance Standards for Antimicrobial Susceptibility Testing. 33rd ed. M100-Ed33. Clinical and Laboratory Standards Institute, Wayne, PA.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

Howard-Anderson J, Hamasaki T, Dai W, Collyar D, Rubin D, Nambiar S, Kinamon T, Hill C, Gelone S, Mariano D, Baba T, Holland, T, Doernberg S, Chambers H, Fowler V, Evans S, Boucherand H; on behalf of the Antibacterial Resistance Leadership Group. “Improving Traditional Registrational Trial End Points: Development and Application of a Desirability of Outcome Ranking End Point for Complicated Urinary Tract Infection Clinical Trials”, Clinical Infectious Diseases, 2023 Feb 1;76(3):e1157-e1165.

Jennison C, Turnbull BW. “Group Sequential Methods with Applications to Clinical Trials,” Chapman & Hall/CRC, Boca Raton, 2000.

Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Statistics in Medicine. 1985;(4)2:213-226.

APPENDIX 1. SECONDARY ESTIMANDS TABLE

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

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

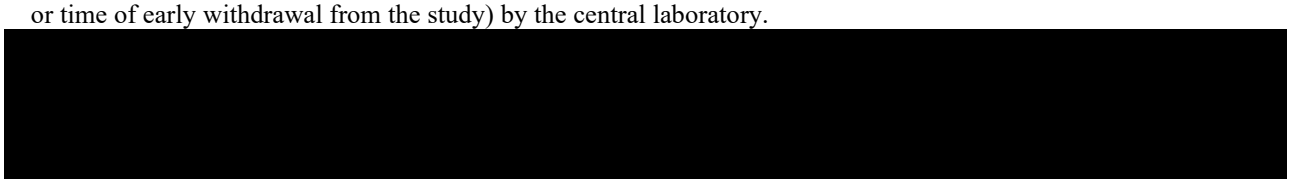
[a] For each of the secondary endpoints the estimand will follow a similar approach to the estimand for the primary endpoint and will use the same general strategies for the ICEs.
CE, Clinically Evaluable; ECGs, electrocardiograms; EOT, End-of-Treatment; ESBL, extended spectrum β-lactamase; FQ-NS, fluoroquinolone-not susceptible; ICE, intercurrent event; LFU, Late Follow-up; ME, Microbiologically Evaluable; micro-ITT, Microbiological Intent-to-Treat; PK, pharmacokinetic; SAE, serious adverse event; TBP, tebipenem; TBP-PI-HBr, tebipenem pivoxil hydrobromide; TEAE, treatment-emergent adverse event; TMP-SMX-R, trimethoprim-sulfamethoxazole-resistant; TOC, Test-of-Cure.

APPENDIX 2. SCHEDULE OF ASSESSMENTS

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

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

[b] Study treatment administration is 7-10 calendar days for all patients. The EOT visit occurs on the calendar day or the day following (+1 day) the last dose of study treatment. All EOT procedures may be performed the day following last dose of study treatment with the exception of the EOT ECGs, which must be performed 1 h (±15 min) after the last dose rather than the following day. Lab assessments that are required on the day of last dose and EOT do not need to be duplicated; for instance, if Day 7 and EOT occur on the same day, the EOT central lab assessment kit should be used in place of Day 7 kit.
[c] TOC visit: Day 17 ±2 days. The procedures at the TOC visit should be performed for all patients including those who prematurely discontinue study treatment.
[d] LFU visit: Day 28 ±2 days. The procedures at the LFU visit should be performed for all patients including those who prematurely discontinue study treatment.
[e] Obtain medical/surgical history, including urological history and any active or inactive conditions diagnosed within the previous 5 years.
[f] Complete physical examinations (C) at Screening, EOT, TOC, and LFU visits consist of skin, head and neck, heart, lung, abdomen (including suprapubic area), extremities, back/flank/costovertebral angle tenderness, and neuromuscular assessments. Focused physical examinations (F) between Day 1 and EOT visits are symptom-based assessments. If Screening visit and Day 1 occur on the same calendar day the focused physical exam on Day 1 is optional.
[g] Vital signs include blood pressure, pulse, respiratory rate, and temperature. Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be collected at Screening, daily Day 1 through EOT (prior to daily IV infusions), TOC, and LFU visits. Body temperature may be taken per the site's preferred method but limited to oral, tympanic, rectal, or core measurements. The same method of measuring a patient's body temperature should be used throughout the study. If Screening visit and Day 1 occur on the same calendar day, repeated vital signs on Day 1 are optional.
[h] Single 12-lead ECGs will be performed for assessment of eligibility at the Screening visit. Repeat single 12-lead ECGs will be performed on Day 1 (after the first dose of oral dose administration) and at the EOT visit (after the last dose of oral dose administration) 1 h (±15 min) and as otherwise clinically indicated after oral dose administration.
[i] Results from the local blood and urine samples are used to determine eligibility (results can be from samples obtained up to 24 h prior to randomization). Assessments include serum creatinine (for CrCl calculation), ALT, AST, total bilirubin, absolute neutrophil count, blood urea nitrogen (or blood urea), urinalysis (for nitrite, LE and WBC in spun or unspun urine). A urine or serum beta human chorionic gonadotropin (β-HCG) pregnancy test (according to local standard-of-care) is performed by the local laboratory on all FOCP at the Screening visit, and if pregnancy is suspected at any time.
[j] Serum creatinine (for CrCl calculation) should be assessed every 3 days for patients with normal renal function at Baseline and at least once daily for patients with moderate renal impairment from the time of first dose until the CrCl stabilizes. If available, weight on the day of the serum creatinine measurement to be used for calculating CrCl.
[k] The central safety laboratory will perform the following evaluations on blood and urine samples: hematology, coagulation, blood chemistry (including L-carnitine), and complete urinalysis. Central safety labs during treatment will be performed on Screening, Day 1 (if the Screening central safety labs are collected on Day 1, the Day 1 labs do not need to be repeated), Day 3, Day 5, Day 7, Day 9 (if still receiving study treatment), EOT, TOC, and LFU visits. In addition, serum β-HCG is performed on all FOCP at the Screening visit and at the patient's final visit (LFU visit or time of early withdrawal from the study) by the central laboratory.



[m] Collect 2 sets of blood cultures (each set is 1 aerobic and 1 anaerobic blood culture bottle for a total of four bottles) from 2 separate venipuncture sites at Screening. Blood cultures should be repeated on the day that a previous (e.g., Baseline) blood culture is determined to be positive (e.g., reveals growth of a uropathogen). Blood cultures should be repeated as necessary until negative blood cultures are obtained.
[n] The tebipenem treatment group will be administered tebipenem 2 × 300 mg film-coated tablets PO for a total of 600 mg q6h (±1 h) plus dummy IV infusion over 30 min q6h (±1 h). The imipenem-cilastatin treatment group will receive imipenem-cilastatin for IV injection, administered as a 500 mg IV infusion over 30 min q6h (±1 h) plus dummy placebo tablets administered PO q6h (±1 h); refer to Figure 1. See Protocol Tables 3 and 4 for dose adjustments in patients with renal impairment.

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

[redacted]

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

APPENDIX 3. PATHOGEN DETERMINATION

Details regarding which organisms will be classified as pathogens or non-pathogens follow.

Bacteria considered causative for cUTI (i.e., pathogens):

1. Enterobacterales
2. *Acinetobacter baumanii*, *Acinetobacter calcoaceticus*, *A. calcoaceticus-A. baumannii* complex, and *Acinetobacter lwoffii*
3. *Pseudomonas aeruginosa*
4. *Enterococcus* spp.
5. *Staphylococcus aureus*
6. *Staphylococcus saprophyticus*

Bacteria considered contaminants and not causative for cUTI:

1. Coagulase-negative staphylococci (with the exception of *S. saprophyticus*)
2. *Corynebacterium* spp. with the exception of *Corynebactrium urealyticum*
3. *Propionibacterium* spp. and other diphtheroids
4. *Bacillus* spp.
5. *Lactobacillus* spp.
6. Alpha-hemolytic streptococci
7. *Gardnerella vaginalis*

Any other bacteria identified in urine at $\geq 10^5$ CFU/mL with no more than two microorganisms identified or identified in blood will be evaluated by a blinded the evaluability review team prior to database lock for causative pathogen determination.

Note that pathogen status as determined above, does not necessarily mean inclusion in the micro-ITT Population (or GP Population). See Section 3 for the uropathogens to include in those populations.

APPENDIX 4. STRATEGY OR METHOD FOR IDENTIFICATION OF TEAES OF SPECIAL INTEREST

All preferred terms have been reviewed from the following standardized MedDRA queries (SMQ):

Topics	SMQ Searches
Liver Disorders	Drug related hepatic disorders (severe events only) SMQ excluding Liver neoplasms, benign (incl cysts and polyps) (SMQ) Liver neoplasms, malignant and unspecified (SMQ)
	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (narrow)
	Hepatitis, non-infectious SMQ (narrow)
	Liver related investigations, signs and symptoms SMQ (narrow)
	Cholestasis and jaundice of hepatic origin SMQ (narrow)
Diarrhea	Pseudomembranous colitis SMQ (narrow) including Diarrhoea (PT)
Hypersensitivity	Hypersensitivity SMQ (narrow) Angioedema SMQ (narrow) Anaphylactic/anaphylactoid shock conditions SMQ (narrow) Severe cutaneous adverse reactions SMQ (narrow) Including PTs: Penile exfoliation Skin exfoliation Lip exfoliation Oral mucosal exfoliation Mucosal exfoliation Throat tightness Vulvovaginal exfoliation Blister Erythema Flushing Hyperaemia Oral mucosal blistering Pruritus Generalised oedema Nasal oedema Oedema Skin oedema Skin swelling Genital ulceration

Topics	SMQ Searches
	Mouth ulceration Mucocutaneous ulceration Mucosal ulceration Skin erosion Stomatitis
Hematological Disorders	Agranulocytosis SMQ (narrow) Including PTs: Haemolytic anaemia Intravascular haemolysis Coombs negative haemolytic anaemia Coombs positive haemolytic anaemia Anaemia Red blood cell count decreased Reticulocyte count increased Reticulocyte percentage increased Reticulocytosis Granulocyte count decreased Granulocytopenia Leukopenia Lymphocyte count decreased Lymphopenia Neutropenia Neutrophil count decreased White blood cell count decreased Thrombocytopenia Platelet count decreased Haematocrit decreased Haemoglobin decreased Haemolysis
Renal Disorders	Acute renal failure SMQ (narrow and broad) Including PTs: Microalbuminuria Nephritis
Seizures	Convulsions SMQ (narrow) including Generalised Convulsive Seizures following immunization SMQ (broad)- selected PTs of: Depressed level of consciousness Clonus Tonic clonic movements

All preferred terms and high-level terms (HLTs) in MedDRA Version 26.0 within each SMQ have been reviewed and non-relevant terms related to drug application or developmental disorders etc. were excluded based on clinical and medical judgment. The preferred term review by the Sponsor was performed without regard for unique preferred terms existing in the TBP-PI-HBr safety database and without regard to the treatment assignment or relationship to study treatment for adverse events existing in the database. This review resulted in a comprehensive list of all MedDRA preferred terms which represent adverse events that the Sponsor considers potentially indicative of the respective topic of special interest and for which there is a reasonable likelihood that the event could be causally related to study treatment (based on a preferred term review only).

The topic of special interest, hypersensitivity, has been further divided into four Sponsor-derived subgroups: 1) serious hypersensitivity reactions, 2) rash, 3) pruritus, urticaria, or angioedema, and 4) other. The topic of special interest, hematologic disorders, has been further divided into four subgroups: 1) low WBC counts, 2) low RBC counts, 3) low platelet counts, and 4) low WBC, RBC, and platelet counts.

The list of preferred terms currently identified by the Sponsor (irrespective of being identified in the TBP-PI-HBr safety database) representing TEAEs for the six topics of special interest is presented in Appendix 5.

APPENDIX 5. TEAES OF SPECIAL INTEREST SEARCH LIST

The preferred terms provided below are based on MedDRA Version 26.0:

Safety Topic	Subgroup	Preferred Term
Liver disorders		ACQUIRED ANTITHROMBIN III DEFICIENCY
		ACQUIRED FACTOR IX DEFICIENCY
		ACQUIRED FACTOR V DEFICIENCY
		ACQUIRED FACTOR VIII DEFICIENCY
		ACQUIRED FACTOR XI DEFICIENCY
		ACQUIRED HEPATOCEREBRAL DEGENERATION
		ACQUIRED PROTEIN S DEFICIENCY
		ACUTE GRAFT VERSUS HOST DISEASE IN LIVER
		ACUTE HEPATIC FAILURE
		ACUTE ON CHRONIC LIVER FAILURE
		ACUTE YELLOW LIVER ATROPHY
		ALANINE AMINOTRANSFERASE ABNORMAL
		ALANINE AMINOTRANSFERASE INCREASED
		ALLERGIC HEPATITIS
		ALLOIMMUNE HEPATITIS
		AMMONIA ABNORMAL
		AMMONIA INCREASED
		ANTI FACTOR X ACTIVITY ABNORMAL
		ANTI FACTOR X ACTIVITY DECREASED
		ANTI FACTOR X ACTIVITY INCREASED
		ANTI-LIVER CYTOSOL ANTIBODY TYPE 1 POSITIVE
		ANTITHROMBIN III DECREASED
		ASCITES
		ASPARTATE AMINOTRANSFERASE ABNORMAL
		ASPARTATE AMINOTRANSFERASE INCREASED
		AST/ALT RATIO ABNORMAL
		ASTERIXIS
		AUTOIMMUNE HEPATITIS
		BACTERASCITES
		BILE ACIDS INCREASED
		BILE OUTPUT ABNORMAL
		BILE OUTPUT DECREASED

Safety Topic	Subgroup	Preferred Term
		BILIARY ASCITES
		BILIARY CIRRHOSIS
		BILIARY FIBROSIS
		BILIRUBIN CONJUGATED ABNORMAL
		BILIRUBIN CONJUGATED INCREASED
		BILIRUBIN EXCRETION DISORDER
		BILIRUBIN URINE PRESENT
		BIOPSY LIVER ABNORMAL
		BLOOD BILIRUBIN ABNORMAL
		BLOOD BILIRUBIN INCREASED
		BLOOD BILIRUBIN UNCONJUGATED INCREASED
		BLOOD FIBRINOGEN ABNORMAL
		BLOOD FIBRINOGEN DECREASED
		BLOOD THROMBIN ABNORMAL
		BLOOD THROMBIN DECREASED
		BLOOD THROMBOPLASTIN ABNORMAL
		BLOOD THROMBOPLASTIN DECREASED
		BROMOSULPHTHALEIN TEST ABNORMAL
		CARDIOHEPATIC SYNDROME
		CHILD-PUGH-TURCOTTE SCORE ABNORMAL
		CHILD-PUGH-TURCOTTE SCORE INCREASED
		CHOLAEMIA
		CHOLESTASIS
		CHOLESTATIC LIVER INJURY
		CHOLESTATIC PRURITUS
		CHRONIC GRAFT VERSUS HOST DISEASE IN LIVER
		CHRONIC HEPATIC FAILURE
		CHRONIC HEPATITIS
		COAGULATION FACTOR DECREASED
		COAGULATION FACTOR IX LEVEL ABNORMAL
		COAGULATION FACTOR IX LEVEL DECREASED
		COAGULATION FACTOR V LEVEL ABNORMAL
		COAGULATION FACTOR V LEVEL DECREASED
		COAGULATION FACTOR VII LEVEL ABNORMAL

Safety Topic	Subgroup	Preferred Term
		COAGULATION FACTOR VII LEVEL DECREASED
		COAGULATION FACTOR X LEVEL ABNORMAL
		COAGULATION FACTOR X LEVEL DECREASED
		COMA HEPATIC
		COMPUTERISED TOMOGRAM LIVER ABNORMAL
		CONGESTIVE HEPATOPATHY
		CRYPTOGENIC CIRRHOSIS
		DIABETIC HEPATOPATHY
		DRUG-INDUCED LIVER INJURY
		DUODENAL VARICES
		FOETOR HEPATICUS
		GALACTOSE ELIMINATION CAPACITY TEST ABNORMAL
		GALACTOSE ELIMINATION CAPACITY TEST DECREASED
		GALLBLADDER VARICES
		GAMMA-GLUTAMYLTRANSFERASE ABNORMAL
		GAMMA-GLUTAMYLTRANSFERASE INCREASED
		GASTRIC VARICEAL INJECTION
		GASTRIC VARICEAL LIGATION
		GASTRIC VARICES
		GASTRIC VARICES HAEMORRHAGE
		GRAFT VERSUS HOST DISEASE IN LIVER
		GUANASE INCREASED
		HEPAPLASTIN ABNORMAL
		HEPAPLASTIN DECREASED
		HEPATECTOMY
		HEPATIC ARTERY FLOW DECREASED
		HEPATIC ATROPHY
		HEPATIC CALCIFICATION
		HEPATIC CIRRHOSIS
		HEPATIC CYTOLYSIS
		HEPATIC ENCEPHALOPATHY
		HEPATIC ENZYME ABNORMAL
		HEPATIC ENZYME DECREASED

Safety Topic	Subgroup	Preferred Term
		HEPATIC ENZYME INCREASED
		HEPATIC FAILURE
		HEPATIC FIBROSIS
		HEPATIC FUNCTION ABNORMAL
		HEPATIC HYDROTHORAX
		HEPATIC HYPERTROPHY
		HEPATIC HYPOPERFUSION
		HEPATIC INFILTRATION EOSINOPHILIC
		HEPATIC LESION
		HEPATIC MASS
		HEPATIC NECROSIS
		HEPATIC PAIN
		HEPATIC SEQUESTRATION
		HEPATIC STEATO-FIBROSIS
		HEPATIC STEATOSIS
		HEPATIC VASCULAR RESISTANCE INCREASED
		HEPATIC VENOUS PRESSURE GRADIENT ABNORMAL
		HEPATIC VENOUS PRESSURE GRADIENT INCREASED
		HEPATITIS
		HEPATITIS ACUTE
		HEPATITIS CHOLESTATIC
		HEPATITIS CHRONIC ACTIVE
		HEPATITIS CHRONIC PERSISTENT
		HEPATITIS FULMINANT
		HEPATITIS TOXIC
		HEPATOBILIARY DISEASE
		HEPATOBILIARY SCAN ABNORMAL
		HEPATOCELLULAR FOAMY CELL SYNDROME
		HEPATOCELLULAR INJURY
		HEPATOMEGALY
		HEPATOPULMONARY SYNDROME
		HEPATORENAL FAILURE
		HEPATORENAL SYNDROME
		HEPATOSPLENOMEGALY

Safety Topic	Subgroup	Preferred Term
		HEPATOTOXICITY
		HYPERAMMONAEMIA
		HYPERBILIRUBINAEMIA
		HYPERCHOLIA
		HYPERFIBRINOLYSIS
		HYPERTRANSAMINASAEMIA
		HYPOCOAGULABLE STATE
		HYPOFIBRINOGENAEMIA
		HYPOPROTHROMBINAEMIA
		HYPOTHROMBINAEMIA
		HYPOTHROMBOPLASTINAEMIA
		ICTERUS INDEX INCREASED
		IMMUNE-MEDIATED CHOLANGITIS
		IMMUNE-MEDIATED HEPATIC DISORDER
		IMMUNE-MEDIATED HEPATITIS
		INTERNATIONAL NORMALISED RATIO ABNORMAL
		INTERNATIONAL NORMALISED RATIO INCREASED
		INTESTINAL VARICES
		INTESTINAL VARICES HAEMORRHAGE
		JAUNDICE
		JAUNDICE CHOLESTATIC
		JAUNDICE HEPATOCELLULAR
		KAYSER-FLEISCHER RING
		LIVER DIALYSIS
		LIVER DISORDER
		LIVER FUNCTION TEST ABNORMAL
		LIVER FUNCTION TEST DECREASED
		LIVER FUNCTION TEST INCREASED
		LIVER INDURATION
		LIVER INJURY
		LIVER OPERATION
		LIVER PALPABLE
		LIVER SCAN ABNORMAL
		LIVER TENDERNESS

Safety Topic	Subgroup	Preferred Term
		LIVER TRANSPLANT
		LIVER-KIDNEY MICROSOMAL ANTIBODY POSITIVE
		MAGNETIC RESONANCE IMAGING HEPATOBILIARY ABNORMAL
		MAGNETIC RESONANCE PROTON DENSITY FAT FRACTION MEASUREMENT
		MITOCHONDRIAL ASPARTATE AMINOTRANSFERASE INCREASED
		MIXED LIVER INJURY
		MOLAR RATIO OF TOTAL BRANCHED-CHAIN AMINO ACID TO TYROSINE
		NODULAR REGENERATIVE HYPERPLASIA
		NON-ALCOHOLIC FATTY LIVER
		NON-ALCOHOLIC STEATOHEPATITIS
		NON-CIRRHOTIC PORTAL HYPERTENSION
		OCULAR ICTERUS
		OEDEMA DUE TO HEPATIC DISEASE
		OESOPHAGEAL VARICES HAEMORRHAGE
		OMENTAL OEDEMA
		PERIHEPATIC DISCOMFORT
		PERIPANCREATIC VARICES
		PORTAL FIBROSIS
		PORTAL HYPERTENSION
		PORTAL HYPERTENSIVE BILIOPATHY
		PORTAL HYPERTENSIVE COLOPATHY
		PORTAL HYPERTENSIVE ENTEROPATHY
		PORTAL HYPERTENSIVE GASTROPATHY
		PORTAL VEIN CAVERNOUS TRANSFORMATION
		PORTAL VEIN DILATATION
		PORTOPULMONARY HYPERTENSION
		PROTEIN C DECREASED
		PROTEIN S ABNORMAL
		PROTEIN S DECREASED
		PROTHROMBIN LEVEL ABNORMAL
		PROTHROMBIN LEVEL DECREASED
		PROTHROMBIN TIME ABNORMAL

Safety Topic	Subgroup	Preferred Term
		PROTHROMBIN TIME PROLONGED
		PROTHROMBIN TIME RATIO ABNORMAL
		PROTHROMBIN TIME RATIO INCREASED
		REGENERATIVE SIDEROTIC HEPATIC NODULE
		RENAL AND LIVER TRANSPLANT
		RETROGRADE PORTAL VEIN FLOW
		REYE'S SYNDROME
		SPLENIC VARICES
		SPLENIC VARICES HAEMORRHAGE
		SPONTANEOUS BACTERIAL PERITONITIS
		STEATOHEPATITIS
		SUBACUTE HEPATIC FAILURE
		SUSPECTED DRUG-INDUCED LIVER INJURY
		THROMBIN TIME ABNORMAL
		THROMBIN TIME PROLONGED
		TRANSAMINASES ABNORMAL
		TRANSAMINASES INCREASED
		ULTRASOUND LIVER ABNORMAL
		URINE BILIRUBIN INCREASED
		VARICES OESOPHAGEAL
		VARICOSE VEINS OF ABDOMINAL WALL
		WHITE NIPPLE SIGN
		X-RAY HEPATOBILIARY ABNORMAL
Diarrhea		ANTIBIOTIC ASSOCIATED COLITIS
		CLOSTRIDIAL INFECTION
		CLOSTRIDIAL SEPSIS
		CLOSTRIDIUM BACTERAEMIA
		CLOSTRIDIUM COLITIS
		CLOSTRIDIUM DIFFICILE COLITIS
		CLOSTRIDIUM DIFFICILE INFECTION
		CLOSTRIDIUM TEST POSITIVE
		DIARRHOEA
		GASTROENTERITIS CLOSTRIDIAL

Safety Topic	Subgroup	Preferred Term
		PSEUDOMEMBRANOUS COLITIS
Hypersensitivity/ Anaphylaxis	Most Serious Hypersensitivity Reactions	AGEP-DRESS OVERLAP
		ANAPHYLACTIC REACTION
		ANAPHYLACTIC SHOCK
		ANAPHYLACTIC TRANSFUSION REACTION
		ANAPHYLACTOID REACTION
		ANAPHYLACTOID SHOCK
		ANAPHYLAXIS TREATMENT
		BRONCHOSPASM
		BULLOUS HAEMORRHAGIC DERMATOSIS
		CIRCULATORY COLLAPSE
		DERMATITIS EXFOLIATIVE GENERALISED
		DIALYSIS MEMBRANE REACTION
		DISTRIBUTIVE SHOCK
		DOCUMENTED HYPERSENSITIVITY TO ADMINISTERED PRODUCT
		DRUG HYPERSENSITIVITY
		DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS
		EPIDERMAL NECROSIS
		ERYTHEMA MULTIFORME
		ERYTHRODERMIC ATOPIC DERMATITIS
		EXFOLIATIVE RASH
		GENERALISED BULLOUS FIXED DRUG ERUPTION
		HYPERSENSITIVITY
		KOUNIS SYNDROME
		LARYNGEAL OEDEMA
		LARYNGOSPASM
		LARYNGOTRACHEAL OEDEMA
		LIP EXFOLIATION
		MUCOSAL EXFOLIATION
		NIKOLSKY'S SIGN
		OCULOMUCOCUTANEOUS SYNDROME

Safety Topic	Subgroup	Preferred Term
		ORAL MUCOSAL EXFOLIATION
		OROPHARYNGEAL OEDEMA
		OROPHARYNGEAL SPASM
		OROPHARYNGEAL SWELLING
		PENILE EXFOLIATION
		PHARYNGEAL OEDEMA
		PHARYNGEAL SWELLING
		PROCEDURAL SHOCK
		SEVERE CUTANEOUS ADVERSE REACTION
		SHOCK
		SHOCK SYMPTOM
		SJS-TEN OVERLAP
		SKIN EXFOLIATION
		STEVENS-JOHNSON SYNDROME
		TARGET SKIN LESION
		THROAT TIGHTNESS
		TONGUE EXFOLIATION
		TOXIC EPIDERMAL NECROLYSIS
		TOXIC SKIN ERUPTION
		TRACHEAL OEDEMA
		TYPE I HYPERSENSITIVITY
		TYPE II HYPERSENSITIVITY
		TYPE III IMMUNE COMPLEX MEDIATED REACTION
		TYPE IV HYPERSENSITIVITY REACTION
		VULVOVAGINAL EXFOLIATION
Hypersensitivity/Anaphylaxis	Rash	ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS
		BLISTER
		BROMODERMA
		DERMATITIS
		DERMATITIS ACNEIFORM
		DERMATITIS ALLERGIC
		DERMATITIS ATOPIC
		DERMATITIS BULLOUS

Safety Topic	Subgroup	Preferred Term
		DERMATITIS CONTACT
		DERMATITIS HERPETIFORMIS
		DERMATITIS INFECTED
		DERMATITIS PSORIASIFORM
		DRUG ERUPTION
		ERYTHEMA
		ERYTHEMA NODOSUM
		FIXED ERUPTION
		FLUSHING
		HAND DERMATITIS
		HYPERAEMIA
		INTERSTITIAL GRANULOMATOUS DERMATITIS
		MUCOCUTANEOUS RASH
		NODULAR RASH
		ORAL MUCOSAL BLISTERING
		OROPHARYNGEAL BLISTERING
		PALISADED NEUTROPHILIC GRANULOMATOUS DERMATITIS
		PENILE DERMATITIS
		PERIORAL DERMATITIS
		PERIORBITAL DERMATITIS
		RASH
		RASH ERYTHEMATOUS
		RASH FOLLICULAR
		RASH MACULAR
		RASH MACULO-PAPULAR
		RASH MACULOVESICULAR
		RASH MORBILLIFORM
		RASH NEONATAL
		RASH PAPULAR
		RASH PAPULOSQUAMOUS
		RASH PRURITIC
		RASH PUSTULAR
		RASH RUBELLIFORM
		RASH SCARLATINIFORM

Safety Topic	Subgroup	Preferred Term
		RASH VESICULAR
		SCROTAL DERMATITIS
		SCROTAL OEDEMA
		SKIN REACTION
		STOMA SITE RASH
		VASCULITIC RASH
		VULVOVAGINAL RASH
Hypersensitivity/Anaphylaxis	Pruritus, Urticaria, or Angioedema	ACQUIRED C1 INHIBITOR DEFICIENCY
		ALLERGIC OEDEMA
		ANGIOEDEMA
		CIRCUMORAL OEDEMA
		CIRCUMORAL SWELLING
		CONJUNCTIVAL OEDEMA
		CORNEAL OEDEMA
		DENNIE-MORGAN FOLD
		EPIGLOTTIC OEDEMA
		EYE OEDEMA
		EYE SWELLING
		EYELID OEDEMA
		FACE OEDEMA
		GENERALISED OEDEMA
		GINGIVAL OEDEMA
		GINGIVAL SWELLING
		HAEMORRHAGIC URTICARIA
		IDIOPATHIC URTICARIA
		INTESTINAL ANGIOEDEMA
		LIMBAL SWELLING
		LIP OEDEMA
		LIP SWELLING
		MOUTH SWELLING
		NASAL OEDEMA
		OCULORESPIRATORY SYNDROME

Safety Topic	Subgroup	Preferred Term
		OEDEMA
		OEDEMA MOUTH
		PALATAL OEDEMA
		PALATAL SWELLLING
		PERIORBITAL OEDEMA
		PERIORBITAL SWELLING
		PRURITUS
		PRURITUS ALLERGIC
		SCLERAL OEDEMA
		SKIN OEDEMA
		SKIN SWELLING
		SOLAR URTICARIA
		SWELLING FACE
		SWELLING OF EYELID
		SWOLLEN TONGUE
		TONGUE OEDEMA
		URTICARIA
		URTICARIA CHOLINERGIC
		URTICARIA CHRONIC
		URTICARIA CONTACT
		URTICARIA PAPULAR
		URTICARIA PHYSICAL
		URTICARIA PIGMENTOSA
		URTICARIA VESICULOSA
		URTICARIAL DERMATITIS
		URTICARIAL VASCULITIS
Hypersensitivity/Anaphylaxis	Other	ALLERGIC BRONCHITIS
		ALLERGIC COLITIS
		ALLERGIC COUGH
		ALLERGIC CYSTITIS
		ALLERGIC EOSINOPHILIA
		ALLERGIC GASTROENTERITIS
		ALLERGIC HEPATITIS

Safety Topic	Subgroup	Preferred Term
		ALLERGIC KERATITIS
		ALLERGIC LYMPHANGITIS
		ALLERGIC OTITIS EXTERNA
		ALLERGIC OTITIS MEDIA
		ALLERGIC PHARYNGITIS
		ALLERGIC REACTION TO EXCIPIENT
		ALLERGIC RESPIRATORY DISEASE
		ALLERGIC RESPIRATORY SYMPTOM
		ALLERGIC SINUSITIS
		ALLERGIC STOMATITIS
		ALLERGY ALERT TEST POSITIVE
		ALLERGY TEST POSITIVE
		ANAL ECZEMA
		ANTIALLERGIC THERAPY
		ARTHRITIS ALLERGIC
		ATOPIC COUGH
		ATOPY
		BLEPHARITIS ALLERGIC
		BLOOD IMMUNOGLOBULIN E ABNORMAL
		BLOOD IMMUNOGLOBULIN E INCREASED
		CHRONIC EOSINOPHILIC RHINOSINUSITIS
		CHRONIC HYPERPLASTIC EOSINOPHILIC SINUSITIS
		CONJUNCTIVITIS ALLERGIC
		CROSS SENSITIVITY REACTION
		CUTANEOUS VASCULITIS
		ECZEMA
		ECZEMA INFANTILE
		ECZEMA NUMMULAR
		ECZEMA VACCINATUM
		ECZEMA VESICULAR
		ECZEMA WEEPING
		ENCEPHALITIS ALLERGIC
		ENCEPHALOPATHY ALLERGIC
		EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Safety Topic	Subgroup	Preferred Term
		EPIDERMOLYSIS
		EPIDERMOLYSIS BULLOSA
		EYE ALLERGY
		GENITAL ULCERATION
		GIANT PAPILLARY CONJUNCTIVITIS
		GLEICH'S SYNDROME
		HENOCH-SCHONLEIN PURPURA
		HENOCH-SCHONLEIN PURPURA NEPHRITIS
		HEPARIN-INDUCED THROMBOCYTOPENIA
		HYPERSENSITIVITY MYOCARDITIS
		HYPERSENSITIVITY PNEUMONITIS
		HYPERSENSITIVITY VASCULITIS
		IMMUNE THROMBOCYTOPENIA
		IMMUNE TOLERANCE INDUCTION
		LARYNGITIS ALLERGIC
		MAST CELL ACTIVATION SYNDROME
		MAST CELL DEGRANULATION PRESENT
		MOUTH ULCERATION
		MUCOCUTANEOUS ULCERATION
		MUCOSAL ULCERATION
		MULTIPLE ALLERGIES
		NEPHRITIS ALLERGIC
		ORAL ALLERGY SYNDROME
		PALPABLE PURPURA
		PATHERGY REACTION
		RADIOALLERGOSORBENT TEST POSITIVE
		REACTION TO EXCIPIENT
		RHINITIS ALLERGIC
		SCLERITIS ALLERGIC
		SERUM SICKNESS
		SERUM SICKNESS-LIKE REACTION
		SKIN EROSION
		SKIN NECROSIS
		SKIN TEST POSITIVE

Safety Topic	Subgroup	Preferred Term
		SOLVENT SENSITIVITY
		STOMA SITE HYPERSENSITIVITY
		STOMATITIS
		SYMMETRICAL DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA
		VAGINAL ULCERATION
		VERNAL KERATOCONJUNCTIVITIS
		VULVAL ECZEMA
		VULVAL ULCERATION
		VULVOVAGINAL ULCERATION
		VULVOVAGINITIS ALLERGIC
Hematological Disorders	Low WBC	AGRANULOCYTOSIS
		FEBRILE NEUTROPENIA
		GRANULOCYTE COUNT DECREASED
		GRANULOCYTOPENIA
		LEUKOPENIA
		LYMPHOCYTE COUNT DECREASED
		LYMPHOPENIA
		NEUTROPENIA
		NEUTROPENIC COLITIS
		NEUTROPENIC INFECTION
		NEUTROPENIC SEPSIS
		NEUTROPHIL COUNT DECREASED
		PURE WHITE CELL APLASIA
		WHITE BLOOD CELL COUNT DECREASED
Hematological Disorders	Low RBC	ANAEMIA
		APLASTIC ANAEMIA
		AUTOIMMUNE APLASTIC ANAEMIA
		COOMBS NEGATIVE HAEMOLYTIC ANAEMIA
		COOMBS POSITIVE HAEMOLYTIC ANAEMIA
		HAEMATOCRIT DECREASED
		HAEMOGLOBIN DECREASED
		HAEMOLYSIS

Safety Topic	Subgroup	Preferred Term
		HAEMOLYTIC ANAEMIA
		INTRAVASCULAR HAEMOLYSIS
		RED BLOOD CELL COUNT DECREASED
		RETICULOCYTE COUNT INCREASED
		RETICULOCYTE PERCENTAGE INCREASED
		RETICULOCYTOSIS
Hematological Disorders	Low platelets	PLATELET COUNT DECREASED
		THROMBOCYTOPENIA
Hematological Disorders	WBC, RBC, and Platelets All Low	BONE MARROW FAILURE
		CYTOPENIA
		FEBRILE BONE MARROW APLASIA
		IMMUNE-MEDIATED CYTOPENIA
		MYELOSUPPRESSION
		PANCYTOPENIA
		PANMYELOPATHY
Renal Disorders		ACUTE KIDNEY INJURY
		ACUTE PHOSPHATE NEPHROPATHY
		ALBUMINURIA
		ANURIA
		AZOTAEMIA
		BLOOD CREATININE ABNORMAL
		BLOOD CREATININE INCREASED
		BLOOD UREA ABNORMAL
		BLOOD UREA INCREASED
		BLOOD UREA NITROGEN/CREATININE RATIO INCREASED
		CONTINUOUS HAEMODIAFILTRATION
		CREATININE RENAL CLEARANCE ABNORMAL
		CREATININE RENAL CLEARANCE DECREASED
		CREATININE URINE ABNORMAL
		CREATININE URINE DECREASED

Safety Topic	Subgroup	Preferred Term
		CRYSTAL NEPHROPATHY
		DIALYSIS
		FRACTIONAL EXCRETION OF SODIUM
		GLOMERULAR FILTRATION RATE ABNORMAL
		GLOMERULAR FILTRATION RATE DECREASED
		HAEMODIALYSIS
		HAEMOFILTRATION
		HYPERCREATININAEMIA
		HYPONATRIURIA
		KIDNEY INJURY MOLECULE-1
		MICROALBUMINURIA
		NEPHRITIS
		NEPHROPATHY TOXIC
		NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN INCREASED
		OEDEMA DUE TO RENAL DISEASE
		OLIGURIA
		PERITONEAL DIALYSIS
		PRERENAL FAILURE
		PROTEIN URINE PRESENT
		PROTEINURIA
		RENAL FAILURE
		RENAL FUNCTION TEST ABNORMAL
		RENAL IMPAIRMENT
		RENAL TRANSPLANT
		RENAL TUBULAR DISORDER
		RENAL TUBULAR DYSFUNCTION
		RENAL TUBULAR INJURY
		RENAL TUBULAR NECROSIS
		SUBACUTE KIDNEY INJURY
		TUBULOINTERSTITIAL NEPHRITIS
		UREA RENAL CLEARANCE DECREASED
		URINE OUTPUT DECREASED
Seizures		ACQUIRED EPILEPTIC APHASIA

Safety Topic	Subgroup	Preferred Term
		ACUTE ENCEPHALITIS WITH REFRACTORY, REPETITIVE PARTIAL SEIZURES
		ALCOHOLIC SEIZURE
		ATONIC SEIZURES
		ATYPICAL BENIGN PARTIAL EPILEPSY
		AUTOMATISM EPILEPTIC
		AUTONOMIC SEIZURE
		BENIGN ROLANDIC EPILEPSY
		CHANGE IN SEIZURE PRESENTATION
		CLONIC CONVULSION
		CLONUS
		CONVULSION IN CHILDHOOD
		CONVULSIONS LOCAL
		CONVULSIVE THRESHOLD LOWERED
		DEJA VU
		DEPRESSED LEVELS OF CONSCIOUSNESS
		DOUBLE CORTEX SYNDROME
		DREAMY STATE
		DRUG WITHDRAWAL CONVULSIONS
		ECLAMPSIA
		EPILEPSIA PARTIALIS CONTINUA
		EPILEPSY
		EPILEPSY SURGERY
		EPILEPSY WITH MYOCLONIC-ATONIC SEIZURES
		EPILEPTIC AURA
		EPILEPTIC PSYCHOSIS
		FACIOBRACHIAL DYSTONIC SEIZURE
		FEBRILE CONVULSION
		FEBRILE INFECTION-RELATED EPILEPSY SYNDROME
		FEBRILE STATUS EPILEPTICUS
		FOCAL DYSCOGNITIVE SEIZURES
		FRONTAL LOBE EPILEPSY
		GELASTIC SEIZURE
		GENERALISED ONSET NON-MOTOR SEIZURE

Safety Topic	Subgroup	Preferred Term
		GENERALISED TONIC-CLONIC SEIZURE
		GREY MATTER HETEROTOPIA
		HEMICONVULSION-HEMIPLEGIA-EPILEPSY SYNDROME
		HYPERGLYCAEMIC SEIZURE
		HYPOCALCAEMIC SEIZURE
		HYPOGLYCAEMIC SEIZURE
		HYPONATRAEMIC SEIZURE
		ICTAL BRADYCARDIA SYNDROME
		ICTAL CENTRAL APNOEA
		ICTAL EPILEPTIC HEADACHE
		IDIOPATHIC GENERALISED EPILEPSY
		INFANTILE SPASMS
		JEAVONS SYNDROME
		JUVENILE ABSENCE EPILEPSY
		JUVENILE MYOCLONIC EPILEPSY
		LENNOX-GASTAUT SYNDROME
		MIGRAINE-TRIGGERED SEIZURE
		MYOCLONIC EPILEPSY
		NEW ONSET REFRACTORY STATUS EPILEPTICUS
		PARIETAL LOBE EPILEPSY
		PARTIAL SEIZURES
		PARTIAL SEIZURES WITH SECONDARY GENERALISATION
		PETIT MAL EPILEPSY
		PHOTOSENSITIVE SEIZURE
		POST STROKE EPILEPSY
		POST STROKE SEIZURE
		POSTICTAL HEADACHE
		POSTICTAL PARALYSIS
		POSTICTAL PSYCHOSIS
		POSTICTAL STATE
		POST-TRAUMATIC EPILEPSY
		SEIZURE
		SEIZURE ANOXIC

Safety Topic	Subgroup	Preferred Term
		SEIZURE CLUSTER
		SEIZURE LIKE PHENOMENA
		SIMPLE PARTIAL SEIZURES
		SLEEP RELATED HYPERMOTOR EPILEPSY
		STATUS EPILEPTICUS
		SUDDEN UNEXPLAINED DEATH IN EPILEPSY
		TARDIVE SEIZURE
		TEMPORAL LOBE EPILEPSY
		TONIC CLONIC MOVEMENTS
		TONIC CONVULSION
		TONIC POSTURING
		TRANSIENT EPILEPTIC AMNESIA
		UNCINATE FITS
		VERTIGINOUS EPILEPSY

RBC, red blood cells; WBC, white blood cells.