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Statistical Analysis Plan
(SAP)

A Phase 3, Randomized, Double-Blind, Multicenter, Comparative Study to Determine the Efficacy and Safety of Cefepime-zidebactam vs. Meropenem in the Treatment of Complicated Urinary Tract Infection or Acute Pyelonephritis in Adults

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SAP APPROVAL FORM

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VERSION HISTORY

Version	Version Date	Description
1.0	09SEP2019	Original signed version
2.0	22OCT2020	Updated based on FDA's comments: • Added expanded mMITT population; • Modified definition of mMITT as a subset of the expanded mMITT population in order to exclude subjects with meropenem-resistant pathogens • Corrected typographical error in the sample size Section 9.6 to match the protocol • Corrrected title to remove mentioning of an oral switch
3.0	12MAR2024	• Updated sample size calculations to correspond to the proposed analysis method • Updated SAP to clearly differentiate analyses (US FDA STIC and EMA EUCAST IC) for the different regulatory regions • Added summaries for handling missing data due to Covid-19 pandemic • Demographic summary categories for BMI and creatinine clearance were reorganized • Added analysis day, 24-hour day calculation, and duration of IV therapy category was reorganized • Added description for baseline definition and baseline pathogens • Added definition of MITT population and pathogen level summary for bateremia in the MITT population • Added summary of concomitant procedures and non-drug therapies • Potentially clinically significance criteria changes in safety labs • Other formatting and/or grammatical changes
4.0	12DEC2024	• Removed hyperlinks causing error message in pdf version of SAP

Version	Version Date	Description
		• Updated table number • Updated missing data handling strategy • Updated demographic and baseline characteristics summary • Updated interpretation of susceptibility results by STIC and EUCAST IC • Added manual review process for antibiotics, systemic antibiotics and diabetes • Added an additional inferential hypothesis per communications with the US FDA • Added a statement of displaying 95% CIs for all efficacy endpoints • Updated subgroup analyses • Replaced urinalysis summary with a listing • Added description for baseline creatinine clearance calculation • Updated PCS criteria for ECG parameters

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AP	Acute pyelonephritis
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
β-HCG	β-human chorionic gonadotropin
BUN	Blood urea nitrogen
CE	Clinically evaluable
CFU	Colony-forming units
CI	Confidence interval
CrCl	Creatinine clearance
CSR	Clinical Study Report
cUTI	Complicated urinary tract infection
CVA	Costovertebral angle
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
e-mMITT	Expanded Microbiologically Modified Intent-to-treat
EOT	End-of-treatment
EUCAST IC	European Committee on Antimicrobial Susceptibility Testing Interpretive Criteria
FEP	Cefepime
FEP-ZID	Cefepime-zidebactam
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous(ly)
LFU	Late Follow-up
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
Mer-R	Meropenem-resistant
MIC	Minimum inhibitory concentration

MITT	Modified Intent-to-treat
mMITT	Microbiologically Modified Intent-to-treat
MN	Miettinen and Nurminen
MRL	Medpace Reference Laboratories
PCS	Potentially clinically significant
PK	Pharmacokinetic
PO	Per os (by mouth)
ROW	Rest of the World
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System organ class
SRC	Safety Review Committee
STIC	Susceptibility Test Interpretive Criteria
TEAE	Treatment-emergent adverse event
TOC	Test-of-cure
ULN	Upper limit of normal
WHO	World Health Organization
ZID	Zidebactam

1. INTRODUCTION

The original Statistical Analysis Plan (SAP Version 1.0, 09SEP2019) was created based on Protocol W-5222-301 (Original version, 04 SEP, 2019) and described in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned Protocol. The SAP was amended (Version 2.0, 22Oct2020) based on comments from the United States Food and Drug Administration (US FDA) on 22SEP2020. A third update following a protocol amendment (Protocol Version 2.0, 14Dec2021) was completed on 15FEB2022 and submitted as a draft version to the US FDA. Details of changes are provided in the Version History section. It is noted that SAP versions 1.0 and 2.0 were prepared prior to enrollment of any subjects into the trial. SAP version 3.0 and 4.0 were signed-off before database lock.

As a consequence of different regulatory requirements and guidance received from drug regulators for the statistical analysis of this study, this SAP includes further refinements of the definition of analyses sets in the protocol. Specifically, subjects with carbapenem-resistant uropathogens will be excluded from the primary efficacy populations. In order to determine carbapenemt susceptibility, two interpretive criteria (IC) will be used. These are the Susceptibility Test Interpretive Criteria (STIC) preferred by the US FDA and the European Committee on Antimicrobial Susceptibility Testing Interpretive Criteria (EUCAST IC).

Analyses based on the STIC will support regulatory requirements from the US FDA. Analyses based on the EUCAST IC will support regulatory requirements in the rest of the world (ROW).

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of this study are:

1. To demonstrate that cefepime-zidebactam (FEP-ZID) is non-inferior to meropenem in overall success (clinical cure and microbiological eradication) in the microbiological Modified Intent-to-treat (mMITT) population at the Test-of-Cure (TOC) visit
2. To assess the overall safety and tolerability of FEP-ZID in the Safety population

2.2. Secondary Objectives

The secondary objectives of this study are:

1. To evaluate the overall outcome at TOC in the Clinically Evaluable (CE) and Microbiological Evaluable (ME) populations
2. To evaluate the overall outcome at End-of-Treatment (EOT) in the mMITT population
3. To evaluate the clinical outcomes at EOT (mMITT population) and at TOC (mMITT, CE and ME populations)
4. To evaluate the microbiological outcome at EOT (mMITT population) and TOC (mMITT, CE and ME populations)

5. To evaluate the by-pathogen overall (mMITT, CE and ME populations) as well as by-pathogen clinical (mMITT and CE populations) and microbiological outcomes (mMITT and ME populations) at TOC
6. To evaluate the clinical outcome at Late Follow-Up (LFU) in the mMITT population
7. To evaluate the pharmacokinetics (PK) of FEP-ZID in adult subjects with complicated urinary tract infections (cUTI) or acute pyelonephritis (AP)

3. STUDY DESIGN

3.1. General Study Design and Plan

This is a Phase 3, randomized, double-blind, multicenter, non-inferiority study to evaluate the efficacy, safety, and tolerability of FEP-ZID vs. meropenem in the treatment of hospitalized adults with cUTI or AP.

Approximately 528 hospitalized adult subjects (≥ 18 years old) diagnosed with cUTI or AP will be enrolled in the study. The diagnosis of cUTI or AP will be based on a combination of clinical symptoms and signs plus the presence of pyuria (Inclusion Criteria 3 and 4).

Subjects will be randomized in a 2:1 ratio via an interactive response technology (IRT) electronic system to receive either FEP-ZID 3 g (2 g cefepime + 1 g zidebactam) IV q8h or meropenem 1 g IV q8h. FEP-ZID will be administered as 2 consecutive infusions of 1.5 g (1 g cefepime + 0.5 g zidebactam), each IV infusion administered over 30 ± 5 minutes, for a total infusion time of 60 ± 10 minutes. Meropenem will be infused over 30 ± 5 minutes, followed by an infusion of normal saline administered over 30 ± 5 minutes, for a total infusion time of 60 ± 10 minutes. Study drug regimens for subjects with renal insufficiency (creatinine clearance (CrCl) 15 to < 60 mL/min) will require dose adjustment (Protocol Section 11.2). Subjects with CrCl < 15 mL/min at screening/baseline are excluded from the study. In the event that a subject's CrCl decreases to between 10 and <15 mL/min, dosing may be continued with the appropriate dose adjustment as shown in Protocol Table 2. For subjects with a decrease in CrCl to <10 mL/min during the study, the decision to continue study drug dosing is to be made on a case by case basis by the Investigator with input from the Medical Monitor. Subjects requiring continuous veno-venous hemofiltration (CVVH) should be discontinued from study drug treatment.

The total duration of treatment with study drug is 7 to 10 days, including for bacteremic subjects. Each subject must remain hospitalized during the study drug treatment period (no outpatient parenteral antibiotic therapy is allowed and no oral switch therapy is permitted). Each subject is expected to complete the study, i.e., all scheduled follow-up visits (i.e., TOC, LFU), including subjects who discontinue study drug prematurely.

All subjects will be required to report their cUTI or AP symptoms on a formal questionnaire which will be administered by trained study center staff at each visit. The Daily Symptom Assessment questionnaire (Protocol Appendix III) will be administered twice at Screening: The Premorbid Symptom Assessment questionnaire will determine whether the subject

normally experiences cUTI or AP symptoms (i.e., in the absence of infection) that may be attributable to other conditions, and the Daily Symptom Assessment questionnaire will capture cUTI/AP symptoms within 24 hours of randomization. To capture changes in symptoms over time, subjects will be administered the Daily Symptom Assessment questionnaire at all visits starting at Screening (i.e., Screening [2 questionnaires as above], Day 1 and each day subject is hospitalized, EOT, TOC, and LFU). The data collected from the questionnaires will be used, in part, to assess the clinical outcome (as described in Protocol Sections 15.2 and 18.3.2).

All organisms isolated from urine and/or blood cultures will be identified to the species level. Urine organisms will be cultured and quantified at the local or regional laboratory, and susceptibility testing of each organism isolated may be performed per local or regional laboratory standards; however, local susceptibility testing will not be available for FEP-ZID. Although local susceptibility testing is not a requirement, when local susceptibility testing indicates possible non-susceptibility to study drug (e.g., intermediate susceptibility or resistance to meropenem) but the subject is stable or clinically improving, the subject should remain on study drug at the Investigator's discretion. In general, decisions around continuation of study drug should be made based on the subject's clinical course, rather than the antimicrobial susceptibility of isolated uropathogens. Investigators should discuss such cases with the Medical Monitor prior to any premature discontinuation of study drug.

If growth of *Enterococcus* spp. or methicillin-resistant *Staphylococcus* spp. is detected from the screening urine or blood culture, narrow-spectrum Gram-positive coverage with an open-label glycopeptide (e.g., vancomycin), oxazolidinone (e.g., linezolid), or daptomycin may be administered concomitantly with blinded study drug at the discretion of the Investigator. Investigators should discuss such cases with the Medical Monitor.

In accordance with the study MRL Laboratory Manual, all potential uropathogens and isolates from non-contaminated blood cultures will be sent to the central laboratory for identification and susceptibility testing, as well as possible additional characterization using molecular testing.

Plasma samples for PK determination will be collected from all subjects (both treatment groups) twice on Day 1 and 4 times on Day 3 (+ 1 day), as described in Protocol Section 17.1 and in the PK Procedures section of the MRL Laboratory Manual; however, only PK samples obtained from the FEP-ZID treatment group will be analyzed.

3.2. Study Population

Adult subjects (≥ 18 years) with cUTI or AP will be enrolled in this study. Based on contemporary Phase 3 cUTI study experience, subjects of at least 65 years of age will constitute approximately 25% of randomized subjects (Wagenlehner, 2015).

3.3. Randomization

Subjects will be randomized in a 2:1 ratio using an IRT electronic system to receive either FEP-ZID or meropenem. Randomization will be stratified by study entry diagnosis (cUTI or

AP) and by geographic region. Subjects who meet diagnosis of both cUTI and AP will be included in the cUTI stratum. At least 30% of subjects will have a diagnosis of cUTI and at least 30% will have AP at study entry. Subjects who received a single dose of an allowed short-acting antibacterial agent within 72 hours prior to randomization (Protocol Appendix I) without documentation of failure on this prior therapy and/or documented uropathogen resistant to this prior therapy, will be capped at a maximum of 15% of enrollment.
After informed consent has been obtained and study eligibility established, an unblinded study pharmacist or designee will obtain the study drug assignment from a computer-generated randomization code using an IRT system. Subjects are considered randomized when the pharmacist or designee receives the IRT-generated treatment assignment regardless of whether the subject actually receives study drug.

3.4. Blinding and Measures to Control Bias

Randomization will be used to minimize the subject selection bias (Section 3.3). This study will be double-blind; the Sponsor, Investigators, study staff participating in subject care or clinical evaluations, and subjects will be blinded to study drug assignment until all subjects have completed the study and the database is locked. There will be a limited unblinded team at the Sponsor and/or Contract Research Organization (CRO) to support the study pharmacists/designees who will have access to treatment assignment information. The unblinded Sponsor and/or CRO team will not be involved in review of the blinded clinical database or decisions regarding subject care. The unblinded team will not share any potentially unblinding information with the blinded individuals until after the database is locked.

The Investigator (or designated Sub-investigator) may unblind a subject's treatment assignment only in the case of an emergency, when the identity of the study drug is essential for the immediate clinical management or welfare of a specific subject. If the subject's clinical status permits, every effort should be made to consult with the Medical Monitor prior to unblinding.

If the blind is broken for a safety reason, the Medical Monitor must be notified immediately and a full written explanation must be provided within 2 calendar days of breaking the blind. The written explanation must not reveal the subject's treatment assignment to the Medical Monitor unless it is important to do so. The Investigator will record in source documentation the date, time, and reason for unblinding the treatment assignment for a given subject.

The Sponsor/designee may break the blind for serious adverse events (SAE) that are unexpected and are believed to be causally related to study drug and that potentially require expedited reporting to regulatory authorities. For more details on how to break the blind, refer to the IRT materials.

3.5. Study Assessments

Table 1 presents the visit schedule and procedures of the study to be conducted at each visit.

Table 1: Schedule of Assessments and Procedures

Visit	Screening/ Baseline	1st Dose	Treatment Period			EOT	TOC	LFU
Procedure	-24 h[a]	Day 1[b]	Day 2	Day 3	Day 4 to EOT[c]	Last day study drug + 24 hours[d]	Day 17 ± 2 days	Day 26 ± 2 days[e]
Informed consent[f]	√							
Inclusion/exclusion criteria	√							
Medical & surgical history and demography[g]	√							
Daily Symptom Assessment Questionnaire[h]	√	√	√	√	√	√	√	√
Physical exam (including CVA tenderness)[i]	√	√	√	√	√	√	√	
Vital signs[j]	√	√	√	√	√	√	√	
12 Lead ECG[k]	√					√	√	√
Randomization		√						
Laboratory Assessments:								
Local laboratory tests for study eligibility[l]	√							
CrCl[m]	√	√	√	√	√	√		
Hematology, serum chemistry and coagulation[n]	√			√		√	√	√
Urinalysis[o]	√			√		√	√	√
Pregnancy test[p]	√						√	
Urine cultures[q]	√			√		√	√	√
Blood cultures[r]	√		√ (as clinically indicated)					
Blood for PK sampling[s]		√		√				
Study drug administration and accountability		√	√	√	√	√		
Adverse Events[t]	√	√	√	√	√	√	√	√
Prior and concomitant medications[u]	√	√	√	√	√	√	√	√
Clinical outcome assessment[v]						√	√	√

Abbreviations: ECG = electrocardiogram; EOT = End-of-Treatment; LFU = Late Follow-up; PK = Pharmacokinetic; TOC = Test-of-Cure.

[a] Following the signing of the informed consent form, all Screening/Baseline evaluations should be completed within 24 hours prior to randomization, with the exception of the urine specimen documenting pyuria or positive culture (if known at the time of screening) which must be collected within 48 hours prior to randomization.

[b] Day 1 is the first day of study drug administration. Subsequent study days are consecutive calendar days. If feasible, Screening and randomization procedures (Screening Visit and Day 1) can be performed on the same day. Standard-of-care laboratory data from within 24 hours prior to randomization can be used as Screening Visit procedures.

[c] Daily assessments are required while subject is hospitalized. If the daily assessment and EOT occur on the same day, only one set of assessments is required for that visit (namely the EOT visit).

[d] EOT is to be conducted on the day of, or within 24 hours following, the last dose of study drug (between Day 7 and Day 10). EOT assessments should also be conducted for any premature withdrawal from study or premature discontinuation of study drug.

[e] LFU is to be conducted on Day 26 ± 2 days. The LFU assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be a clinical cure at TOC (Protocol Section 14.2 and Protocol Table 4), met microbiological eradication (Protocol Section 15.2.3 and Protocol Table 9) and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the TOC visit; otherwise, the visit must be conducted in person (see Protocol Section 12.8). This visit should be conducted in person if the TOC visit was missed.

[f] Written and signed informed consent must be obtained before any protocol assessment is performed.

[g] Record only significant or relevant medical history within the past 5 years.

[h] Administer the Daily Symptom Assessment questionnaire (Protocol Appendix III) at all visits starting at Screening. Note: At the Screening Visit, 2 questionnaires are required: the Premorbid Symptom Assessment questionnaire to assess symptoms prior to the onset of current cUTI or AP and the Daily Symptom Assessment questionnaire to assess the symptoms of the cUTI or AP within 24 hours of randomization (Baseline assessment).

[i] Physical exam—consisting of general appearance, skin, eyes, ears, nose, throat, lungs, heart, abdomen, urogenital, back, extremities, lymph nodes, vascular, and neurological exams—will be conducted at Screening. A directed physical exam based on Baseline findings will be performed daily between Day 1 and EOT and a full physical exam will be performed at EOT and TOC. Every physical exam must include an evaluation of costovertebral angle (CVA) tenderness.

[j] Vital signs—including body temperature (oral, tympanic, or rectal), blood pressure, heart rate, and respiratory rate —will be collected at Screening and daily between Day 1 and EOT, and at TOC. Weight and height will also be collected at the Screening Visit. Most abnormal vital sign values (if more than one taken) will be recorded in the electronic Case Report Form (eCRF), and the same method of temperature collection should be used across visits for consistency, whenever possible.

[k] A 12-lead ECG will be performed at Screening and EOT. A 12-lead ECG will be performed at TOC or LFU only if prior ECG(s) showed any clinically-significant abnormality.

[l] At Screening, local laboratory evaluations required for assessing subject eligibility include: Serum transaminase (ALT and AST), total bilirubin, and alkaline phosphatase levels, serum creatinine, peripheral absolute neutrophil count, platelet count, and urinalysis (with urine microscopy if leukocyte esterase is negative or only one '+' positive) in all subjects, and serum or urine β-HCG in females. Urine must also be collected for local laboratory urine culture; however, culture results (e.g., growth of eligible uropathogens) are not required prior to randomization. If azotemia is suspected, obtain BUN (or urea). Refer to Protocol Section 12.1 for information on tests performed as standard of care.

[m] Dose adjustment based on CrCl is required for administration of study drug in subjects with a CrCl 15 to < 60 mL/min (Protocol Section 11.2). Between Screening and EOT, local serum creatinine must be obtained for CrCl determination at least once daily, or more frequently as needed.

[n] Blood will be collected for central laboratory testing at the Screening, Day 3, EOT, and TOC visits (full list of central laboratory tests available in Protocol Appendix II); blood will also be collected for central laboratory testing at LFU in subjects with clinically significant laboratory abnormalities noted at or after the TOC visit.

[o] Urine will be sent to the central laboratory for urinalysis at the Screening, Day 3, EOT, and TOC visits (full list of analytes available in Protocol Appendix II); urine will also be collected for central laboratory testing at LFU in subjects with clinically significant urine abnormalities noted at or after the TOC visit.

[p] For females only at Screening, a negative urine or serum pregnancy test performed locally is required to confirm study eligibility. In addition, blood will be collected from all female subjects for serum β-HCG pregnancy test by the central laboratory at the Screening and TOC visits.

[q] An adequate clean-catch urine specimen for culture (or other appropriate method to collect a urine culture that minimizes risk of bacterial contamination) should be obtained at the Screening, Day 3, EOT, and TOC visits for local or regional laboratory microbiological assessment. If a subject is enrolled after taking prior antibiotics per the exception criteria mentioned in Exclusion Criterion 2, the screening urine culture should be taken as close to randomization as possible (within 2 hours prior to randomization, if possible). At LFU, a urine culture must be obtained in subjects who meet the criteria for an in-person visit. At any point in the study if a subject is deemed a clinical failure or if clinically indicated, a urine specimen for culture should be obtained prior to the start of any rescue antimicrobial therapy.

[r] At the screening/baseline visit two sets of blood samples for culture from two separate sterile venipuncture sites will be collected. If any screening/baseline blood cultures are positive and not considered contaminated, two sets of repeat blood cultures should be obtained (for local or regional laboratory microbiological assessment) until negative. To avoid unnecessary blood draws, the Investigator may wait until the result of the prior blood culture is known before performing the next blood culture (Protocol Section 13.2).

[s] Blood samples for PK analysis will be collected from all subjects on Day 1 (two samples: within 15 minutes and 1 to 2 hours after end of infusion of first dose (that is, the end of infusion of the 2nd container of study drug on Day 1) and on Day 3 (+ 1 day) - four samples taken around one of the three study drug infusions on that day at the following time points: Immediately prior to dosing (up to 30 minutes before the start of IV administration) and 1 to 2 hours, 3 to 4 hours, and 5 to 7 hours after the end of IV administration of study drug.

[t] AEs and SAEs will be collected from signing of the informed consent to the LFU visit.

[u] Antimicrobial medications that have been administered within 14 days and non-antimicrobial medications (including herbal supplements, vitamins and over-the-counter medications) that have been administered within 7 days prior to the date of signing the informed consent and during the Screening visit will be recorded in the eCRF. All medications administered after the first dose of study drug and up to the LFU visit must be recorded in the eCRF.

[v] The investigator will assess the clinical outcome, in part, from the responses on the Daily Symptom Assessment questionnaire.

4. SAMPLE SIZE JUSTIFICATION

This study is designed to demonstrate non-inferiority of FEP-ZID 3 g (2 g cefepime + 1 g zidebactam) IV q8h compared with meropenem 1 g IV q8h for the primary endpoint: the proportion of subjects with overall success at TOC in the mMITT population. A non-inferiority margin of 15.0% will be used, based on historic data regarding the treatment effect of antibiotics.

Estimates of overall success rates and numbers of subjects in the mMITT population come from the literature. A Phase 3 study in cUTI and AP found overall success rates at TOC in the mMITT population of 68.4% and 76.9% for the treatment arms (ceftolozane/tazobactam and levofloxacin, group, respectively), with an evaluability rate of approximately 75% (Wagenlehner, 2015). A more recent study in cUTI including AP found overall success rates at TOC in the mMITT population of 74.5% and 70.3% for the treatment arms (meropenem/vaborbactam and piperacillin/tazobactam, respectively), with an evaluability rate of approximately 70% (Kaye, 2018). Thus, it is reasonable to assume a 70% overall success rate at TOC and 75% evaluability rate for determination of the sample size and the enrolment projections.

Using a 15.0% non-inferiority margin, one-sided alpha of 0.025, 85% power, an overall success rate of 70% in each treatment group at TOC, and the sample size methodology based on the Farrington-Manning sample size approach for the Miettinen and Nurminen (MN) method, a total of 396 subjects are required in the mMITT population. Assuming 75% of subjects will be evaluable for the mMITT population, a total of approximately 528 subjects diagnosed with cUTI or AP will be randomized in the study (ITT population), using a 2:1 allocation ratio (352 subjects in the FEP-ZID arm, 176 in the meropenem arm).

5. EFFICACY ENDPOINTS AND ASSESSMENT

5.1. Efficacy Variables

Primary efficacy variable:

- Overall outcome (composite of clinical outcome and microbiological outcome) at TOC (mMITT population)

Secondary efficacy variables:

- Overall outcome at TOC (CE and ME population)
- Overall outcome at EOT (mMITT population)
- Clinical outcomes at EOT (mMITT population) and TOC (mMITT, CE and ME populations)
- Microbiological outcomes at EOT (mMITT population) and TOC (mMITT, CE and ME populations)
- By-pathogen overall (mMITT, CE and ME populations), clinical (mMITT and CE populations) and microbiological (mMITT and ME populations) outcomes at TOC
- Clinical outcome at LFU (mMITT population)

5.2. Efficacy Assessments

5.2.1. Overall Outcome

The by–subject overall outcome will be obtained at the EOT and TOC visits. The assessment obtained at TOC will be the primary efficacy variable and the assessment at EOT will be a secondary efficacy variable.

The by-subject overall outcome is a composite outcome that is determined programmatically based on the clinical outcome and microbiological outcome as detailed in Table 2.

Table 2: Overall Outcome at EOT and TOC

Outcome	***Definition***
Overall Success	Criteria met for clinical response at EOT (Table 4) or clinical cure at TOC (Table 5) AND overall microbiological eradication at the corresponding visit (Table 7)
Overall Failure	Criteria met for clinical non-response at EOT (Table 4) or clinical failure at TOC (Table 5) OR overall microbiological persistence (Table 7). An overall outcome of failure at EOT will be carried forward to the TOC visit
Overall Indeterminate	Study data are missing for evaluation of clinical or microbiological outcome for any reason and the subject cannot otherwise be declared an overall failure at the given visit
Abbreviations: EOT = End-of-Treatment; TOC = Test-of-cure	

The determination of the overall outcome based on these rules is illustrated below.

Table 3: Overall Outcome by Results for each Component

Clinical Outcome	***Microbiological Outcome***		
	Eradication	***Persistence***	***Indeterminate***
Response/Cure	Success	Failure	Indeterminate
Non-Response/ Failure	Failure	Failure	Failure
Indeterminate	Indeterminate	Failure	Indeterminate

By-pathogen overall outcome at TOC will be determined based on the composite of the subject's clinical outcome at TOC (Table 5) and by-pathogen microbiological outcome (Table 7).

5.2.2. Clinical Outcome

The clinical outcome at EOT and TOC will be determined by the investigator as described in Table 4 and Table 5 (see also Protocol Section 14.2).

Table 4: Clinical Outcome Assessments at EOT

Outcome	Definition
Clinical Response	Meets all of the following criteria: • Complete resolution[1] (or return to premorbid state) of the cUTI or AP symptoms[2] that were present at Screening, except flank pain (if present), which should show at least one grade improvement (e.g., from severe to moderate, moderate to mild, or mild to absent) • No new cUTI or AP symptoms[2]
Clinical Non-response[3]	Meets any of the following criteria: • Change from baseline in cUTI or AP symptoms does not meet the criteria for clinical response • Required alternative rescue antibacterial treatment for cUTI or AP prior to assessment • Developed a TEAE that required discontinuation of study therapy and the cUTI or AP required additional antibiotic therapy • Death from any cause prior to the assessment
Indeterminate	• Study data are missing for evaluation of clinical response or non-response for any reason Note: A clinical outcome of indeterminate will not be carried forward to subsequent visits.

Abbreviations: AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOT = End-of-Treatment; TEAE = treatment-emergent adverse event.
[1]: If a symptom presents with the same severity at both premorbid and baseline assessments and is no worse at the EOT visit, then the symptom will be considered resolved or returned to premorbid state.
[2]: For the determination of clinical outcome only the following cUTI or AP symptoms will be used: flank pain, lower abdominal/suprapubic/pelvic pain, dysuria, urinary frequency, and/or urinary urgency.
[3]: A clinical non-response at EOT will be carried forward to TOC.

Table 5: Clinical Outcome Assessments at TOC

Outcome	Definition
Clinical Cure	Meets all of the following criteria: • Complete resolution[1] (or return to premorbid state) of the cUTI or AP symptoms[2] that were present at Screening • No new cUTI or AP symptoms[2]
Clinical Failure[3]	Meets any of the following criteria: • Change from baseline in cUTI or AP symptoms does not meet the criteria for clinical cure • Required antibacterial treatment for cUTI or AP after EOT and prior to TOC assessment • Death from any cause prior to assessment
Indeterminate	• Study data are missing for evaluation of clinical cure or failure at the assessment visit for any reason

Abbreviations: AP = acute pyelonephritis; cUTI = complicated urinary tract infection; TOC = Test-of-cure.
[1]: If a symptom presents with the same severity at both premorbid and baseline assessments and is no worse at the TOC visit, then the symptom will be considered resolved or returned to premorbid state.
[2]: For the determination of clinical outcome only the following cUTI or AP symptoms will be used: flank pain, lower abdominal/suprapubic/pelvic pain, dysuria, urinary frequency, and/or urinary urgency.
[3]: A clinical non-response at EOT will be carried forward to TOC.

By-pathogen clinical outcome (cure, failure or indeterminate) at TOC will be determined based on the subject's clinical outcomes (Table 5) at TOC i.e., if the per-subject clinical outcome is cure/failure/indeterminate then the clinical outcome for each baseline pathogen will be cure/failure/indeterminate, respectively.

5.2.3. Clinical Outcome at LFU Visit

For subjects with an outcome of clinical cure at the TOC visit, the Investigator will assess the clinical outcome at the LFU visit (Day 26 ±2 days) as described in Table 6.

Table 6: Clinical Outcome at LFU

Outcome	Definition
Sustained Clinical Cure	Meets all of the following criteria: • Met criteria for clinical cure at TOC • No cUTI or AP symptom1 more severe than the premorbid level
Clinical Failure	Meets any of the following criteria: • Relapse of any cUTI or AP symptom[1] (i.e. more severe than the premorbid level) • New cUTI or AP symptom[1] • Required systemic antibacterial treatment between TOC and LFU for cUTI or AP • Death from any cause between TOC and LFU
Clinical Indeterminate	• Study data are missing for evaluation of sustained clinical cure at LFU for any reason

Abbreviations: AP = acute pyelonephritis; cUTI = complicated urinary tract infection; LFU = Late Follow-up; TOC = Test-of-cure.
[1]: For the determination of clinical outcome only the following cUTI or AP symptoms will be used: flank pain, lower abdominal/suprapubic/pelvic pain, dysuria, urinary frequency, and/or urinary urgency.

5.2.4. Microbiological Outcome

A programmatic determination of by-pathogen and by-subject microbiological outcome (eradication, persistence, or indeterminate) will be made at EOT and TOC.

The by-subject microbiological outcome at EOT and TOC will be determined based on individual outcomes for each baseline pathogen; specifically, for a subject to have an outcome of microbiological eradication, each baseline uropathogen identified must be eradicated. If the outcome for any pathogen is microbiological persistence, the by-subject microbiological outcome will be microbiological persistence. By-pathogen and by-subject microbiological outcome categories at EOT and TOC are detailed in Table 7.

Table 7: By-Pathogen and By-Subject Microbiological Outcome Categories at EOT and TOC

Outcome[1]	***Definition***
Microbiological Eradication	By-pathogen microbiological eradication: Baseline uropathogen reduced to $< 10^3$ CFU/mL at the given visit

	By-subject microbiological eradication: All baseline uropathogens reduced to < 10^3 CFU/mL at the given visit
Microbiological Persistence	By-pathogen microbiological persistence: Assessment urine culture grows ≥ 10^3 CFU/mL of the same baseline uropathogen at the given visit By-subject microbiological persistence: At least one baseline uropathogen had an outcome of persistence at the given visit Microbiological persistence at EOT will carry forward to TOC
Microbiological Indeterminate	Unavailable urine culture or the culture cannot be interpreted for any reason at the given visit
Abbreviations: CFU = Colony-forming units; EOT = End-of-Treatment; TOC = Test-of-cure. [1]: Only results obtained from interpretable urine cultures will be used in the determinations of microbiological outcomes. For subjects with a uropathogen that was also present in the blood, blood cultures will not be used in the determination of microbiological outcomes.	

5.2.5. Emergent Infections

Infection caused by pathogens first appearing after Screening (emergent infections) will be programmatically categorized as either superinfections or new infections as defined in Table 8. Emergent infections will not be considered in the determination of by-subject or by-pathogen microbiological outcome analyses described above.

Table 8: Emergent Infections

Category	***Definition***
Superinfection	Isolation of a new uropathogen(s) meeting the same criteria as for baseline uropathogens (other than the original cUTI or AP pathogen[s]) from an appropriate post-baseline urine culture, which is accompanied by cUTI or AP symptoms[1] requiring alternative systemic antimicrobial therapy during the period *up to and including* EOT (i.e., was a clinical non-response at EOT)
New infection	Isolation of a new uropathogen(s) meeting the same criteria as for baseline uropathogens (other than the original cUTI or AP pathogen[s]) from an appropriate post-baseline urine culture which is accompanied by cUTI or AP symptoms[1] requiring alternative systemic antimicrobial therapy during the period *after* EOT (i.e., was a clinical failure at TOC or LFU)
Abbreviations: AP = acute pyelonephritis; cUTI = complicated urinary tract infection; EOT = End-of-Treatment; TOC = Test-of-cure; LFU = Late Follow-up. [1]: For the determination of clinical outcome only the following cUTI or AP symptoms will be used: flank pain, lower abdominal/suprapubic/pelvic pain, dysuria, urinary frequency, and/or urinary urgency.	

6. SAFETY ASSESSMENTS

6.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily

have to have a causal relationship with this treatment. In clinical studies, an AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease occurring at any time after the subject has signed informed consent, even if no study therapy has been administered.

Adverse events may also include post-treatment complications that occur as a result of protocol-mandated procedures (eg invasive procedures such as venipuncture and biopsy). Pre-existing (before signing the Informed Consent Form [ICF]) events that increase in severity or change in nature during, or as a consequence of, use of a medicinal product in a human clinical study will also be considered AEs.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

All AEs and serious AE (SAEs) will be recorded and reported from the signing of the ICF to the time of the LFU Visit and included in data listings with both verbatim and coded/preferred term included.

6.2. Safety Assessments

Safety parameters will be monitored according to standard medical practice and guidelines for administration of study drug. Vital sign assessments (temperature, blood pressure, heart rate, and respiratory rate), medical history, prior and concomitant medications, height, weight, and physical examination findings will be conducted at the specified time points outlined in the Schedule of Assessments and Procedures (Table 1).

6.3. Laboratory Assessments

Blood samples for clinical laboratory tests and blood/urine samples for pregnancy tests will be collected at baseline and throughout the study according to the Schedule of Assessments and Procedures (Table 1).

6.4. Safety Review Committee

An independent Safety Review Committee (SRC) will be utilized in this study. The SRC will perform periodic reviews of unblinded accumulated safety data from the study at intervals specified in the SRC Charter. The SRC will also evaluate the impact of the COVID-19 pandemic on the study conduct. The Sponsor will remain blinded to all data presented to, and reviewed by, the SRC. Details are provided in the SRC charter.

7. PHARMACOKINETIC EVALUATION

Efforts will be made to obtain PK samples from all subjects twice on Day 1 and four times on Day 3 (+ 1 day), as described below. Only samples obtained from subjects who are randomized to receive FEP-ZID will be analyzed. However, in order to protect the blind, PK blood draws will be performed for all subjects. Blood samples for PK analyses will be collected at the following times:

- Day 1:
    - Within 15 minutes (min) after the end of the infusion of the first dose of study drug; and
    - 1 to 2 hours (h) after the end of the infusion of the first dose of study drug (i.e. the end of administration of the second IV infusion)
- Day 3 (+ 1 day)—around one of the three IV study drug administrations that is convenient for plasma sample collection—at the following time points:
    - Within 30 min before starting IV administration
    - 1 to 2 h after the end of the infusion of study drug (i.e. the end of administration of the second IV infusion)
    - 3 to 4 h after the end of the infusion of study drug (i.e. the end of administration of the second IV infusion)
    - 5 to 7 h after the end of the infusion of study drug (i.e. the end of administration of the second IV infusion)

8. ANALYSIS POPULATIONS

8.1. Intent-to-Treat Population (ITT)

The ITT population will include all subjects who were randomized, regardless of whether the subject actually received study drug. For analyses based on the ITT population, subjects will be analyzed according to the assigned study treatment.

8.2. Modified Intent-to-Treat Population (MITT)

The MITT population will include all subjects in the ITT population who received any amount of study drug (FEP-ZID or meropenem). Subjects will be analyzed according to the assigned study treatment.

8.3. Safety Population

The safety population will include all randomized subjects who receive any amount of study drug (FEP-ZID or meropenem). Subjects will be analyzed according to the treatment actually received.

8.4. Expanded Microbiological Modified Intent-to-Treat Population (e-mMITT)

The expanded mMITT (e-mMITT) population will include all ITT subjects who received any amount of study drug (MITT) and have at least one eligible uropathogen from an interpretable, baseline urine sample (see Protocol Section 13.1).

Sole infection with *Enterococcus* spp. and/or methicillin-resistant staphylococci will exclude subjects from this population.

8.5. Microbiological Modified Intent-to-Treat Population defined using the STIC (mMITT-STIC)

The mMITT-STIC population will be a subset of the e-mMITT. Subjects whose index cUTI or AP is caused by a carbapenem-resistant (or not applicable) pathogen (per STIC), solely or in combination with susceptible pathogens, will be excluded from this population.

8.6. Microbiological Modified Intent-to-Treat Population defined using the EUCAST IC (mMITT-EUCAST IC)

The mMITT-EUCAST IC population will be a subset of the e-mMITT. Subjects whose index cUTI or AP is caused by a carbapenem-resistant (or not applicable) pathogen (per EUCAST IC), solely or in combination with susceptible pathogens, will be excluded from this population.

8.7. Clinically-Evaluable Population defined using the STIC (CE-STIC)

The CE-STIC populations will include all mMITT-STIC subjects who follow important components of the trial.

In order to be included in the CE populations, subjects must meet all of the following criteria:

- Meet key Inclusion Criteria, including the clinical disease criteria for cUTI or AP (Inclusion Criteria #3A or 3B, respectively) and pyuria (Inclusion Criterion #4)
- Do not meet key Exclusion Criteria (Exclusion Criteria #1, 2, 3, 5, 6, or 9)
- The TOC visit occurred within a window of 17 ± 3 days from the date of randomization unless the subject was deemed a clinical failure prior to this visit
- Do not receive non-study, potentially-effective against the baseline uropathogen(s), systemic antibacterial therapy between Day 1 and the assessment TOC (except in cases of treatment failure)
- Do not have a clinical outcome of indeterminate at the TOC visit
- Must have a completed Daily Symptom Assessment questionnaire at Baseline and the TOC visit
- Received at least 80% of the intended doses of randomized study drug therapy (based on dates/times of first and last study drug administration) (Note: subjects treated opposite the randomization will not be considered to have received the intended dose)
- Received at least 48 hours of study drug therapy in order to be considered an evaluable clinical failure and at least 72 hours of study drug therapy in order to be considered an evaluable clinical success

- Did not have any other major protocol deviations that may confound efficacy assessments at TOC

8.8. Clinically-Evaluable Population defined using the EUCAST IC (CE-EUCAST IC)

The CE-EUCAST IC population will include all mMITT-EUCAST IC subjects who follow important components of the trial as listed in the previous section 8.6.

8.9. Microbiologically-Evaluable Population defined using the STIC (ME-STIC)

The ME-STIC population will include all subjects in the CE-STIC population who do not have a microbiological outcome of indeterminate at TOC (see Table 7) and had the microbiological determination at TOC visit within the protocol-defined window. However, any interpretable urine culture that is positive (i.e., grows a study qualifying uropathogen) and is obtained at EOT through TOC will be carried forward to TOC.

8.10. Microbiologically-Evaluable Population defined using the EUCAST IC (ME-EUCAST IC)

The ME-EUCAST IC population will include all subjects in the CE-EUCAST IC population who do not have a microbiological outcome of indeterminate at TOC (see Table 7) and had the microbiological determination at TOC visit within the protocol-defined window. However, any interpretable urine culture that is positive (i.e., grows a study qualifying uropathogen) and is obtained at EOT through TOC will be carried forward to TOC.

8.11. Pharmacokinetic (PK) Population

The PK population includes all subjects in the Safety population who received at least 1 dose of FEP-ZID and had at least 1 analyzable plasma PK sample.

9. STATISTICAL ANALYSIS

9.1. General Statistical Considerations

9.1.1. General Analysis Approach

All data will be summarized separately by treatment group (FEP-ZID or meropenem). Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables for each study drug. Frequency distributions (counts and percentages) will be presented for categorical variables. Exploratory analyses may also be performed.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (eg, standard deviation) will be displayed to two decimal places greater than the original value (up to three decimal place). All analyses will be performed using SAS® Version 9.4 or higher.

9.1.2. Handling of Dropouts and Missing Data

Every effort will be made to collect all data at the specified times.

Two categories of missing data will be identified. These will be defined based on whether or not the missing efficacy data are due to the COVID-19 pandemic.

9.1.2.1 **Missing Data not due to the COVID-19 Pandemic-General**

Missing data not due to the COVID-19 pandemic will be handled as follows:

- All missing and partial dates for events occurring after randomization or for medications received after randomization will be queried for a value. In cases of missing or incomplete dates (eg, AE and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRF will be presented in the data listings;
- Missing times, severity, and causality for adverse events will be queried for a value. No imputations will be made for missing times. Adverse events with a missing time will be considered treatment emergent if the date is on or after the first dose of study drug, adverse events with missing severity will be considered severe and adverse events with a missing relationship to study drug will be considered related to study drug;
- Missing dates and time of prior and/or concomitant systemic antibiotics will be queried for a value. In cases of missing or incomplete dates/times, the missing component(s) will be assumed as the most conservative value possible. For example, a prior antibiotic missing exact times will be assumed to have been received within 72 hours if the available dates make this plausible. If dates are missing then it will be considered both prior and concomitant;
- For the primary efficacy outcome measure, subjects with missing data for either component (microbiological or clinical) will be considered an indeterminate response provided the subject cannot otherwise be declared a treatment failure (see Table 2). By definition, subjects with an indeterminate overall response are included in the denominator for analyses in the mMITT (EUCAST and STIC) population and are excluded from the ME population. Subjects with overall indeterminate outcome due to an indeterminate clinical (but not microbiological) outcome will be excluded from the CE (EUCAST and STIC) population. Analyses described in Section 9.3.1.1 will assess the robustness of the analysis of the primary efficacy outcome;
- For the clinical outcome at TOC, subjects with missing data will be considered an indeterminate response (see Table 4 and Table 5). By definition, subjects with an

indeterminate response are included in the denominator for analyses in the mMITT (EUCAST and STIC) population and are excluded from the CE population (EUCAST and STIC). However, if the relevant symptoms are all absent at EOT, TOC and LFU visits, a subject's clinical outcome will be response/cure irrespective of whether premorbid symptom assessments are missing. For subjects that are missing either the premorbid or the baseline assessments and subjects that cannot be declared a clinical non-response/failure at EOT, TOC or LFU visits, the programmatically derived clinical outcome would be indeterminate;

- For the microbiological outcome at TOC, subjects with missing data (eg uninterpretable urine culture) will be considered an indeterminate response (see Table 7). Microbiological outcomes will not be presumed from clinical outcomes. By definition, subjects with an indeterminate response are included in the denominator for analyses in the mMITT (EUCAST IC and STIC) population and are excluded from the ME (EUCAST IC and STIC) population. Subjects with indeterminate clinical outcome are also excluded from the ME (EUCAST IC and STIC) population. Subjects with indeterminate clinical outcome are also excluded from the ME (EUCAST IC and STIC) population;
- Missing values for other variables will not be imputed and only observed values will be used in data analyses and presentations.

9.1.2.2 **Missing Data Due to the COVID-19 Pandemic -Efficacy**

The study will be monitored for missing data due to the COVID-19 pandemic. Efficacy data from participants at sites closed for a period of time due to the COVID-19 pandemic will be excluded from efficacy analyses, provided the participant was randomized and had or would have had efficacy assessments during the closure period. Participants at sites that are permanently closed will be similarly handled.

Subjects withdrawn before the closure period (irrespective of whether the reasons were related/unrelated to the COVID-19 pandemic) or that were known to have an unfavorable response at the TOC visit at the time of site closure will be handled as described in Section 9.1.2.1.

Efficacy data from subjects excluded from analyses due to the COVID-19 pandemic will be listed only.

Study enrollment may be extended to avoid the loss of statistical power due to these excluded subjects, with prior approvals by the Ethics Committees/Institutional Review Boards and regulatory authorities, as applicable.

Data from individual participants (whether assessments are missing or not) who report discontinuation of study drug or study participation due to the COVID-19 pandemic but where the site has not been closed (temporarily or permanently) will not be excluded from analyses and any missing assessment will be handled as described in Section 9.1.2.1. A sensitivity analysis for the primary efficacy variable excluding these subjects will be conducted.

9.1.3. Baseline Definition

For microbiological data, baseline pathogen(s) are determined from the urine culture collected prior to the first dose of study drug. Urine cultures collected on the day of first dose with missing times of collection may be allowed as baseline cultures if a predose culture is

not available for any reason. To be considered interpretable, the baseline urine culture must grow < 3 bacterial organisms. Organism(s) from interpretable urine cultures that grow $\geq 10^5$ CFU/mL will be considered potential baseline uropathogen(s). Organism(s) that grow $\geq 10^3$ and $<10^5$ CFU/mL in baseline urine culture and are also present in baseline blood cultures (±72 hours from the baseline urine culture and no later than first dose date) will also be considered potential baseline uropathogen(s) (see Protocol Section 13.1 for details). Baseline urine culture needs to be collected before the first dose of study drug (unless time of collection is missing as noted above). Baseline blood culture may be collected after the first dose time of study drug but on the same day.

If ≥ 3 bacterial organisms are identified, the culture will be considered contaminated regardless of colony count, unless one of the isolates that grows at $\geq 10^3$ CFU/mL in the urine is also isolated from a baseline blood culture. Only the pathogen(s) cultured from both urine and blood will be considered potential baseline pathogen(s).

For all efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to the first dose of study drug or randomization if not dosed.

9.1.4. Analysis Day

Two methods will be used to define the analysis day/study day. For the first approach the analysis day/study day will be determined based on calendar dates only. For the second approach, the analysis day/study day will be based on 24-hour intervals starting with the date and time of first dose.

Analysis day (calendar day) will be calculated from the date of first dose of study drug, Analysis Day (calendar day) = Date – Date of First Dose (+1 if Date >= Date of First Dose). The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

Similarly, analysis day (24-hour day, for exposure and compliance calculation in SAP section 9.2.9 Dosing and Treatment Exposure) will be calculated from the date/time of the first dose of study drug. There will be no Day 0 or negative days in 24-hour day calculation if dosed.

9.2. Study Subjects

9.2.1. Subject Disposition

Subject disposition (enrollment and discontinuations from the study), study drug administered, premature discontinuations from study drug, withdrawals from the study will be summarized by treatment group in the ITT, e-mMITT and mMITT-STIC and mMITT-EUCAST IC populations.

The following subject disposition categories will be included in the summary:

- Subjects who were randomized
- Subjects who were randomized and treated
- Subjects who were randomized and treated per the assigned study drug

- Subjects who were randomized and not treated
- Subjects who completed the treatment as reported by the investigator
- Subjects who did not complete the treatment as reported by the investigator
- Subjects who completed the study through LFU visit
- Subjects who did not complete the study
    - Subject who did not complete study due to COVID-19 pandemic-related site closure
- Subjects with a TOC visit
- Subjects with a report of missing efficacy assessments at the TOC visit and the COVID-19 pandemic was a contributory factor
- Subjects excluded from efficacy analyses due to COVID-19 pandemic-related site closures

For subjects who did not complete the treatment, and subjects who did not complete the study, a summary will be provided by reason of discontinuation. In addition, for subjects with a missing efficacy assessments at the TOC visit for which the COVID-19 pandemic was a contributory factor, the reasons that it was a contributory factor will be tabulated.

The total number of subjects for each defined population will be tabulated in the ITT Population. Reasons for exclusions from analyses populations will be tabulated. Tallies of the number of subjects in each analyses population by study site within each geographic region will be generated in the ITT Population.

9.2.2. Protocol Deviations

The number of subjects with Clinical Study Report (CSR) reportable protocol deviations will be summarized by treatment group in the ITT, e-mMITT, mMITT-STIC and mMITT-EUCAST IC populations. A listing of CSR reportable protocol deviations due to the COVID-19 pandemic will be provided. Site level PDs (if any) will not be included in by-subject PD summary or listing unless the same PD is recorded at subject level.

9.2.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics including height, weight, age (as a continuous variable and categorized as < 65, ≥ 65, 65 - <75 and ≥ 75 years), sex, race (American Indian or Alaskan Native, Asian non-Chinese, Asian Chinese, Black or African American, Native Hawaiian or Other Pacific Islander, White or Other), ethnicity, creatinine clearance (using central laboratory results, or use local laboratory if results from the central laboratory are missing)) [as a continuous variable and categorized by degree of renal impairment as (<15 (very severe), 15 to <30 (severe), 30 to <60 (moderate), 60 to <90 (mild) and ≥90 (normal) mL/min as well as (Definition 2) <140 vs ≥140 (Augmented Renal Clearance)), BMI (continuous as well as categorized as <18.5 (underweight), 18.5 to <25 (normal), 25 to <30 (overweight) and ≥30 kg/m^2 (obese)) and the presence of bacteremia at baseline will be

summarized by treatment group in the ITT, e-mMITT, mMITT-STIC and mMITT-EUCAST IC populations. In addition, the presence of bacteremia in the MITT population will be summarized.

Summaries of enrollment by entry diagnosis (cUTI or AP) and geographic region for each treatment group will also be presented in the e-mMITT and mMITT (STIC and EUCAST IC) populations. Entry diagnosis collected in EDC will be used in subject disease characteristics analyses, stratified sensitivity analyses, supportive analyses and subgroup analyses.

For each entry diagnosis, cUTI and AP, baseline signs and symptoms [i.e., documented fever, nausea or vomiting, dysuria/increased urinary frequency or urgency, lower abdominal/suprapubic/pelvic pain (cUTI only), acute flank pain (onset 7 days prior to randomization, AP only), CVA tenderness (AP only)] and evidence of pyuria (i.e., positive leukocyte esterase on urinalysis, WBC ≥ 10 cells/mm^3 in unspun urine or WBC count ≥ 10 cells/high-power field in urine sediment) will be tabulated in the mMITT population. In addition, for cUTI, risk factors will be summarized (i.e., intermittent bladder catheterization, functional or anatomical abnormality, complete or partial obstructive uropathy, azotemia, history of urinary retention in men). If a catheter is reported, the following will also be tabulated: catheter placed on same day of baseline urine sample, catheter placed > 1 day prior to baseline urine sample and catheter removed at the time of baseline urine sample.

9.2.4. Pre-morbid and Baseline Clinical Signs and Symptoms

The number and percentage of subjects with each sign and symptom present at premorbid and also at baseline (fever; nausea or vomiting; dysuria, increased urinary frequency or urinary urgency; lower abdominal, suprapubic, or pelvic pain; acute flank pain; and costovertebral angle tenderness on physical examination) will be tabulated in the e-mMITT and mMITT (STIC and EUCAST IC) populations.

9.2.5. Baseline Pathogens

The number of subjects with pathogenic organisms identified from the baseline urine culture or urine and blood cultures will be summarized by Gram stain type (Gram-positive and Gram-negative bacteria), and by species within Gram stain type and relevant antibiotic resistant phenotypes (eg, extended-spectrum beta-lactamase (ESBL)-screen positive phenotype, (STIC defined as MIC of ≥ 2 mg/L for ceftriaxone, ceftazidime, and/ or aztreonam; cefepime-resistant [MIC of ≥ 2 mg/L for *Enterobacterales (*formerly known as *Enterobacteriaceae)*, and ≥ 16 mg/L for *P. aeruginosa*]; EUCAST defined as MIC of ≥ 4 mg/L for ceftriaxone, ceftazidime, and/ or aztreonam; cefepime-resistant [MIC of ≥ 8 mg/L for *Enterobacterales (*formerly known as *Enterobacteriaceae)*, and ≥ 16 mg/L for *P. aeruginosa*]) and treatment group in the e-mMITT, mMITT (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations. In addition, results for the *Acinetobacter baumanii-cloacae* complex as a group will be presented.

The identification (genus and species) of organisms isolated will be done by the local and central laboratories. In cases of discrepancies between the two, the central laboratory identification will be used. Baseline pathogens are determined by a combination of

programmatical derivation of qualifying baseline pathogens as defined in protocol section 13.1 followed by manual review of the study pathogens identified by the clinical/microbiological review team at the CRO and confirmed by the sponsor before unblinding. Carbapenem-resistance will be tested using meropenem.

The number and percentage of subjects with:

- monomicrobial Gram-negative (including sole carbapenem-resistant pathogen),
- monomicrobial Gram positive (eg, subjects with monomicrobial *Staphylococcus saprophyticus* or methicillin-susceptible *Staphylococcus aureus* [MSSA] (using the cefoxtin disk test (< 21 mm) as surrogate marker for oxacillin resistance),
- polymicrobial Gram-negative (including with and without carbapenem-resistant pathogen),
- polymicrobial Gram-positive,
- mixed (Gram-positive and Gram-negative (with and without carbapenem-resistant pathogens)) or
- any carbapenem-resistant Gram-negative pathogen

infection will also be provided in the e-mMITT and mMITT (STIC and EUCAST IC) populations.

Summaries of baseline organisms based on the Source (Urine, Urine and Blood or Blood only) will be presented. This includes organisms that are present in both urine and blood sample (i.e. uropathogens), organisms present in the baseline blood culture only (i.e. not uropathogens and not considered contaminants) and organisms present in the baseline urine culture only (i.e. uropathogens). The per-pathogen summaries of organisms identified from subjects with bacteremia (irrespective of whether the organisn is also a uropathogen) will be provided by treatment group in the MITT, e-mMITT and mMITT (STIC and EUCAST IC) populations. In addition, the per-pathogen summaries of organisms identified in subjects with bacteremias that are also uropathogens will be provided by treatment group in the e-mMITT and mMITT (STIC and EUCAST IC) populations. The per-pathogen summaries of organisms identified in the blood only will be provided by treatment group in the MITT population.

For each treatment group (FEP-ZID and meropenem), the MIC summary data (MIC_{50}, MIC_{90}, and MIC range and number of isolates tested) for baseline pathogens (isolated from urine only or urine and blood), including cefepime-resistant phenotypes, will be summarized by treatment group in the e-mMITT, mMITT (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations. The MIC_{50} and MIC_{90} will only be calculated for pathogens isolated at least 10 times within either treatment group.

Tabulations by treatment group of the number of baseline pathogens [n (%)] by Interpretation of Susceptibility (susceptible, intermediate, resistant and not applicable/unknown) will be provided using current FDA STIC and using the current EUCAST IC in the e-mMITT, mMITT and ME populations. For each interpretive criteria (FDA STIC and EUCAST IC), subjects with organisms that are either resistant or not applicable/unknown are excluded from the respective analyses set. A listing of MIC values and disk diffusion zone diameters for FEP-ZID and meropenem will be provided with corresponding interpretations by FDA STIC and EUCAST.

9.2.6. Medical and Surgical History

Medical and surgical history terms will be coded using MedDRA. Medical and surgical history will be summarized by treatment group and MedDRA system organ class (SOC) and preferred term (PT) in the Safety, e-mMITT and mMITT (STIC and EUCAST IC) populations.

All medical and surgical history will be listed by subject.

9.2.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications will include medications used before the first dose of study drug. Any medications used on or after the first dose of study drug will be included as concomitant medications. Medications taken both prior and after first dose of study drug will be classed as both prior and concomitant.

The number and percentage of subjects taking prior medications within 14 days of enrollment will be summarized in the Safety population by Anatomical Therapeutic Chemical (ATC) class and preferred name (PN) for each treatment group. For the prior systemic antibacterial therapy, these summaries will also be generated in the mMITT (STIC and EUCAST IC) population.

In addition, the number and percentage of subjects taking prior antimicrobials within 72 h (48h if enrolled under Protocol V1.0) of enrollment will be summarized in the mMITT (STIC and EUCAST IC) population by ATC class and PN for each treatment group. Summaries of subjects who received potentially-effective systemic antibacterial therapy within 72 hours prior to randomization, received a single dose of allowed short acting antibiotic (without documentation of failure on this prior therapy and/or documented uropathogen resistant to this prior therapy, capped at 15% of enrollment), received > 72 hours of a prior antibiotic therapy but signs and symptoms worsened, or cUTI or AP caused by a pathogen that is not susceptible to the prior antibiotic therapy (ies), as collected in EDC, will be presented in the mMITT (STIC and EUCAST IC) analyses set.

The number and percentage of subjects taking concomitant medications will be summarized in the same manner described above (i.e., by ATC class and PN) in the Safety population. In addition, the number and percentage of subjects taking concomitant systemic antibiotics will also be summarized in the mMITT (STIC and EUCAST IC) population.

The classifications of medications as systemic antibiotics is done by manual review of the medications reported in the EDC (after coding), including indication and route by the clinical review team at the CRO and confirmed by the sponsor before unblinding.

All prior and concomitant medications and procedures will be listed by subject.

9.2.8. Concomitant Procedures and Non-Drug Therapies

Concomitant procedures and non-drug therapies will be coded using MedDRA. The number and percentage of subjects taking concomitant procedures and non-drug therapies will be summarized by treatment group and MedDRA coded indication and procedure/non-drug therapy in the Safety and mMITT (STIC and EUCAST IC) populations.

All concomitant procedures and non-drug therapies will be listed by subject.

9.2.9. Dosing and Treatment Exposure

Duration of IV therapy will be calculated in two manners, using calendar days as well as 24-hour day (See Section 9.1.4). The duration of IV therapy (calendar days) will be calculated as the last dose date of IV therapy minus the first dose date of IV therapy +1. The duration of IV study drug (24-hour days) is calculated as the last dose date/time of IV therapy minus the first dose date/time of IV therapy and round up to whole days by 24 hours. In addition, for each mode of calculation, contingency tables will be provided to show the number and percentage of subjects in each treatment group with duration of IV therapy in the following categories: ≤ 3, > 3 - 6 days, 7 - < 10 days, 10 days, 11 days, and > 11 days (days will be rounded to the nearest integer).

The compliance rate to IV therapy will be calculated as the total number of doses received divided by the total number of doses expected then multiplied by 100. The total number of expected doses is the number of medication days (measured using 24-hour days) multiplied by the number of expected doses per day. The number of expected doses per (24-hour) day will be 3 for subjects with baseline CrCl > 50 ml/min, 4 for subjects with baseline CrCl 30 to ≤ 50 mL/min, 2 for subjects with baseline CrCl 10 to < 30 mL/min and undefined for ≤ 10 mL/min (see Protocol Section 11.2, Table 2). If a subject receives ≤ 48 hours of IV therapy, the expected doses will be calculated assuming the subject received full 48 hours therapy. If a subject receives > 10 (24-hour) days IV therapy, the expected doses will be calculated assuming the subject received 10 (24-hour) days of therapy.

Percent compliance to IV therapy will be calculated using the following formula:

$$\%\text{compliance} = \frac{\text{no. of doses received}*100}{\text{expected doses per day} * \text{total number of medication (24-hour) days}}$$

The number and percentage of subjects with % compliance: < 80%, 80-120% and > 120% will be tabulated in each treatment group. Compliance by degree of Renal Impairment at baseline (Definition 1: <15, 15 to <30, 30 to <60, 60 to <90 or ≥90 as well as Definition 2: ≥140 (Augmented Renal Clearance) vs <140) will also be presented. The compliance tabulations will be generated using results from the local laboratory at baseline .

All summaries will be provided for the Safety and mMITT (STIC and EUCAST IC) populations.

9.3. Efficacy Analyses

Efficacy analyses will be performed on the e-mMITT (hierarchical superiority hypothesis only, See Section 9.3.1), mMITT (STIC and EUCAST IC), CE (STIC and EUCAST IC), and ME(STIC and EUCAST IC) populations. Subjects in the e-mMITT and mMITT (STIC and EUCAST IC) populations will be analyzed according to the assigned treatment group irrespective of the treatment actually received. Subjects in the CE (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations receiving incorrect study drug will be excluded from analyses in these populations.

9.3.1. Primary Efficacy Analyses

The primary efficacy endpoint for the US-FDA is the proportion of subjects with an overall success (clinical cure and microbiologic eradication) at TOC in the mMITT-STIC population.

For the ROW, the primary efficacy endpoint is the proportion of subjects with an overall success (clinical cure and microbiologic eradication) at TOC in the mMITT-EUCAST IC population.

Subjects will be categorized as overall success, overall failure (where failure at EOT due to either microbiological persistence and /or clinical failure at EOT is carried forward to TOC), or overall indeterminate at TOC as described in Section 5.2.1. Subjects with missing data or who are lost to follow-up for reasons unrelated to the COVI-19 pandemic (see Section 9.1.2.1) or if related to COVID-19, from sites that do not experienced closure (see Section 9.1.2.2) are defined as indeterminate for the primary analysis and are included in the denominator for the calculation of overall success rate. Thus, these subjects with an indeterminate outcome are effectively counted as failures for the primary analysis. Subjects with missing data due to the COVID-19 pandemic (as described in Section 9.1.2.2) will be excluded from these analyses.

The number and percentage of subjects in each treatment group in each outcome category will be reported. The null (H_0) and alternative (H_1) hypotheses are the following:

$$H_0: \pi_1 - \pi_2 \leq -0.150 \text{ vs } H_1: \pi_1 - \pi_2 > -0.150$$

Where:

π_1 = the proportion of subjects with overall success at TOC in the FEP-ZID treatment group,

π_2 = the proportion of subjects with overall success at TOC in the meropenem treatment group,

and the constant -0.150 is the non-inferiority margin.

The non-inferiority hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. This is based on the lower limit of the 2-sided 95% confidence intervals (CIs) for the observed difference in the proportion of subjects with overall success (FEP-ZID group minus the meropenem group) at the TOC visit. The primary analysis is based on a CI computed using the method of (unstratified) MN.

Primary Inferential Hypothesis

US-FDA,

If the lower limit of the 2-sided 95% CI for the difference between treatment groups at TOC in the mMITT-ST IC population is greater than -0.150 the null hypotheses will be rejected and the non-inferiority of FEP-ZID to meropenem will be concluded based on the primary efficacy endpoint.

ROW,

If the lower limit of the 2-sided 95% CI for the difference between treatment groups at TOC in the mMITT-EUCAST IC population is greater than -0.150 the null hypotheses will be rejected and the non-inferiority of FEP-ZID to meropenem will be concluded based on the primary efficacy endpoint.

Secondary Inferential Hypotheses

US-FDA

If the primary hypotheses of noninferiority of FEP-ZID versus meropenem is accepted, the following two hypotheses will be tested in the sequential order given at the 0.025 significance level. At each step, if a null hypotesis cannot be rejected, no further testing will be done and all subsequent null hypothesies will not be rejected.

- FEP-ZID is noninferior to meropenem with a noninferiority margin of 10.0% . The null and alternative hypothesis are: H_0: $\pi_1 - \pi_2 \leq -0.100$ vs H_1: $\pi_1 - \pi_2 > -0.100$. Noninferiority will be concluded is the lower limit of the 2- sided 95% CI for the difference between treatment groups at TOC in the mMITT-ST IC population is greater than -0.100

- FEP-ZID is superior to meropenem. The null and alternative hypothesis are: H_0: $\pi_1 - \pi_2 \leq 0.00$ vs H_1: $\pi_1 - \pi_2 > 0.00$. Superiority will be concluded if the lower bound of the 95% CI for the treatment difference in overall success at TOC in the e-mMITT population is greater than 0.000.

ROW

If the primary hypotheses of noninferiority of FEP-ZID versus meropenem in the mMITT-EUCAST IC population, superiority of FEP-ZID versus meropenem will be tested in the same manner as described for the US-FDA.

Results will be presented as percentages in the summary tables rounded to 2 decimal places.

9.3.1.1. Additional Analyses of the Primary Efficacy Outcomes

Various analyses will be conducted to assess the robustness of the primary efficacy analysis using the MN approach described above. Missing data will be handled as described in Section 9.1.2.

These include:

1. Sensitivity Analyses
    a. Comparison of treatment groups in terms of the difference in the proportion of subjects with overall success at TOC in the mMITT (STIC and EUCAST IC) excluding subjects with indeterminate outcome at the given visit due to the COVID-19 pandemic from sites that were not closed (see Section 9.1.2.2),
    b. Comparison of treatment groups in terms of the difference in the proportion of subjects with overall success (composite of clinical and microbiological outcomes) at TOC in the mMITT (STIC and EUCAST IC) population where the clinical outcome is determined programmatically using only the Daily Symptom Assessment questionnaire
    c. Comparison of treatment groups in terms of the difference between treatment groups in the proportion of subjects with overall success (composite of clinical and microbiological outcomes) at TOC in the mMITT (STIC and EUCAST IC) population where the clinical outcome is determined programmatically using the Daily Symptom Assessment questionnaire as well as the assessment of CVA tenderness obtained from the physical exams at baseline and at TOC. In these analyses, any baseline CVA tenderness present at baseline must be fully resolved at the TOC visit to be considered an overall success at this visit. Rules for the derivation of this outcome in combination with the flank pain are as follows:

FP present (Mild, Moderate or Severe) at baseline, CVA tenderness absent (Not Done, Missing, No Sign) at baseline			
	FP resolved (No Symptom) at TOC	**FP not resolved (Mild, Moderate or Severe) at TOC**	**FP missing at TOC**
CVA tenderness resolved (No Sign) at TOC	Cure	Failure	Indeterminate
CVA tenderness not resolved (Mild, Moderate or Severe) at TOC	Failure	Failure	Failure
CVA tenderness missing or Not Done at TOC	Cure	Failure	Indeterminate

FP absent (No Symptom or missing) at baseline, CVA tenderness present (Mild, Moderate or Severe) at baseline			
	FP resolved (No Symptom) at TOC	**FP not resolved (Mild, Moderate or Severe) at TOC**	**FP missing at TOC**
CVA tenderness resolved (No Sign) at TOC	Cure	Failure	Cure
CVA tenderness not resolved (Mild, Moderate or Severe) at TOC	Failure	Failure	Failure
CVA tenderness missing or Not Done at TOC	Indeterminate	Failure	Indeterminate

FP absent (No Symptom or missing) at baseline, CVA tenderness absent (Not Done, Missing, No Sign) at baseline			
	FP resolved (No Symptom) at TOC	**FP not resolved (Mild, Moderate or Severe) at TOC**	**FP missing at TOC**
CVA tenderness resolved (No Sign) at TOC	Cure	Failure	Cure
CVA tenderness not resolved (Mild, Moderate or Severe) at TOC	Failure	Failure	Failure
CVA tenderness missing or Not Done at TOC	Cure	Failure	Indeterminate

d. Analysis conducted using the MN statistic stratified by the randomization factors: entry diagnosis (cUTI or AP) collected in EDC and geographical region in the mMITT (STIC and EUCAST IC)population

e. Analysis in which subjects with an indeterminate overall outcome at TOC are imputed as overall success. The 2-sided 95% CI for the difference in overall success will be calculated in the mMITT (STIC and EUCAST IC) population

2. Secondary Analyses

a. Comparison of treatment groups in terms of the difference (FEP-ZID minus Meropenem) in the proportion of subjects with overall success at TOC in the CE (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations. These are further discussed in Section 9.3.2

3. Supportive Analyses

a. Assessment of the overall outcome separately across the stratification factors: diagnosis (cUTI or AP) and geographical region. For each geographic region

and diagnosis stratum, a 2-sided 95% CI for the observed difference (FEP-ZID minus meropenem) in the proportion of subjects with overall success will be calculated in the mMITT (STIC and EUCAST IC) population

9.3.2. Secondary Efficacy Analyses

The secondary analysis variables are listed in Section 5.1. For each by subject secondary efficacy outcome, the number and percentage of subjects with each response [eg, for the clinical outcome at TOC response is either cure, failure or indeterminate (where subjects with missing assessments will be handled as described in Section 9.1.2)] will be summarized by treatment group. For all efficacy endpoints, the difference between treatment groups in the proportion of subjects with favorable response (eg, for the clinical outcome: the difference between treatment groups in proportions of subjects with clinical cure at TOC) and corresponding 2-sided 95% CI will be presented using the same methodology as for the primary analyses but without the inferential interpretation. These summaries will be done for the outcomes/visits/population combinations shown in Table 9.

Table 9: Secondary Analysis (by-subject) Variable by Visit and Key Analyses Populations

Analysis Variable[1]	*Visit*	*Population**			
		e-mMITT	***mMITT***	***CE (at TOC)***	***ME (at TOC)***
Overall Outcome	EOT		X		
	TOC	x	NA (primary)	X	X
Clinical Outcome	EOT		X		
	TOC		X	X	X
	LFU[2]		X		
Microbiological Outcome	EOT		X		
	TOC		X	X	X

[1]: The Overall, Clinical, and Microbiological Outcomes will be determined as described in Sections 5.2.1, 5.2.2 and 5.2.3.
[2]: Only subjects in the mMITT population who are clinical cures at TOC will be included in the evaluations at LFU
*For the mMITT, CE and ME, this includes definitions based on the STIC and EUCAST IC

For the by-subject microbiological outcome at TOC in the mMITT (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations, additional evaluations will be conducted using alternative definitions for the by-pathogen microbiological eradication and microbiological persistence outcomes. For these evaluations, the by-subject microbiological outcome at TOC will be microbiological eradication if all baseline uropathogens are reduced to $< 10^2$ CFU/mL (considered sterile as anything less is below the limits of detection). Likewise, the by-subject microbiological outcome at TOC will be microbiological persistence if at least one baseline

uropathogen grows ≥ 10^2 CFU/mL. Subjects with unavailable or uninterpretable urine cultures will have an indeterminate by-subject microbiological outcome at TOC.

An evaluation in which subjects with super-infections as well as new infections are considered microbiological failures at TOC will be done in the mMITT (STIC and EUCAST IC) population. For these evaluations, subjects with super-infections at EOT will be carried forward to the TOC visit.

The by-pathogen overall success rate at TOC (as described in Section 5.2.3) will be summarized in the mMITT (STIC and EUCAST IC), CE (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations. The by-pathogen clinical cure rate at TOC will be summarized in the mMITT (STIC and EUCAST IC) and CE (STIC and EUCAST IC) populations and the by-pathogen microbiological eradication rates at TOC will be summarized in the mMITT (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations. For each outcome, the number and percentage of subjects will be tabulated by treatment group and baseline uropathogen. By-pathogen summaries will be done by Gram negative and Gram positive organisms. Within the Gram negative organism, summaries will be presented with *Enterobacterales* grouped together. The *Enterobacterales* will be further categorized as ESBL-positive as well as cefepime-resistant (as defined in Section 9.2.5). In addition, results for the *Acinetobacter baumanii-cloacae* complex as a group will be presented.

By-subject overall, clinical and microbiological outcomes at TOC for subjects with cefepime-resistant uropathogens will be generated in the mMITT (STIC and EUCAST IC) population.

By-subject overall, clinical and microbiological outcomes for subjects with carbapenem-resistant Gram-negative pathogens will also be generated at TOC in the e-mMITT population.

For subjects with bacteremia, the by-subject clinical outcomes at TOC (MITT, mMITT (STIC and EUCAST IC) populations) will also be evaluated. For summaries based on the MITT population, all subjects with bacteremia at baseline will be included irrespective of whether the organism was also a uropathogen. For summaries based on the mMITT (STIC and EUCAST IC) population, subjects with bacteremia where the organism is also a uropathogen will be included.

By-pathogen overall outcomes by MIC (mg/L) to FEP-ZID and also to meropenem will be summarized by treatment group for the TOC visit in the e-mMITT, mMITT (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations. In addition, by-pathogen overall outcomes by cefepime MIC (mg/L) will be generated by treatment group in the mMITT (STIC and EUCAST IC) and ME (STIC and EUCAST IC) populations. These summaries will be done for all baseline uropathogens. Gram negative uropathogens that belong to the *Enterobacterales* order will be categorized as such and by-pathogen results will be presented for the *Enterobacterales* order. In addition, results for the *Acinetobacter baumanii-cloacae* complex as a group will be presented.

By-pathogen overall, clinical and microbiological outcomes at TOC in subjects with bacteremia where the causative pathogen was also a uropathogen will be presented for the mMITT (STIC and EUCAST IC) population.

The number and percentage of subjects with a superinfection and new infection will be presented by treatment group and species in the mMITT (STIC and EUCAST IC) populations.

A listing of pathogens with decreased susceptibility (defined as a ≥ 4-fold increase in MIC to drug received relative to that of the baseline uropathogens) will be generated as well as a listing of subjects who are overall failures at TOC in the mMITT (STIC and EUCAST IC) population. Fold change is calculated as the log base 2 of the ratio of the post-baseline MIC value to the baseline MIC value and rounded to the nearest integer.

9.3.3. Subgroup Analyses

The following subgroups based on baseline characteristics will be used for subgroup analyses:

- Age (years) group (< 65, 65 to < 75, and ≥ 75; < 65 vs ≥ 65; < 75 vs ≥ 75)
- Sex (Male or Female)
- Race (American Indian or Alaskan Native, Asian non-Chinese, Asian Chinese, Black or African American, Native Hawaiian or Other Pacific Islander, White or Other)
- BMI (kg/m^2) categories (<18.5 (underweight), 18.5 to <25 (normal), 25 to <30 (overweight) and ≥30 (obese))
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino or other)
- Geographic region (per stratification)
- Entry diagnosis (cUTI or AP) collected in EDC
- Baseline Creatinine clearance (mL/min) group (Definition 1: <15, 15 to <30, 30 to <60, 60 to <90 or ≥90 as well as Definition 2: ≥140 (Augmented Renal Clearance) vs <140) (Baseline creatinine clearance values obtained from the central laboratory will be used. For subjects without a value obtained from the central laboratory, the baseline value from the local laboratory will be used, if available)
- Subjects with and without prior potentially effective systemic antibiotics
- Subjects with and without presence of SIRS (Systemic Inflammatory System Response) defined as the presence at baseline of at least 2 of:
    - Body temperature > 38°C or < 36°C
    - Heart rate > 90 beats/min
    - Respiratory rate > 20 breaths/min
    - WBC < 4,000 cells/mm^3 or > 12,000 cells/mm^3

- Subjects with No Foreign Body, Removable Foreign Body or Non-removable Foreign Body. Among subjects with Removable Foreign Boday, the subgroup with urinary catheters will be also summarized
- Subjects with and without diabetes (based on a manual review of coded medical history PTs by the clinical review team at the CRO and confirmed by the sponsor before unblinding)
- Presence (yes or no) of bacteremia at baselinewhere the organism is also a uropathogen

Subgroups will be evaluated using the overall outcome at TOC (by mMITT STIC and EUCAST IC populations). 2-sided 95% CIs will be presented for subgroups with more than 15 subjects per treatment arm but without the inferential interpretation, and forest plots will be generated for corresponding subgroup analyses.

9.4. Safety Analyses

All safety summaries and analyses will be performed on the Safety population, All subjects will be summarized according to the treatment actually received.

Safety will be evaluated by presenting summaries of treatment-emergent AEs, vital signs, laboratory evaluations (hematology, chemistry and coagulation parameters) and ECG parameters. Urinalysis parameters will be listed only. For each safety parameter, unless otherwise stated, the last assessment made prior to the first administration of study drug will be used as the baseline value for all analyses.

9.4.1. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an adverse event that occurs during or after the first administration of study drug and up through the LFU visit or pre-existing conditions that increases in severity after the first administration of study drug (as recorded on the CRFs).

An overview of TEAEs will be provided summarizing the incidence of subjects with the following:

- Any TEAEs
- Study drug-related TEAEs
- Maximum severity of TEAEs
- Maximum severity of study drug-related TEAEs
- Any TEAE leading to death
- Serious TEAEs
- Drug-related serious TEAEs
- Discontinuation of study drug due to TEAEs
- Discontinuation of study drug due to drug-related TEAEs

The number and percentage of subjects who experienced at least one TEAE will be summarized by treatment group, MedDRA system organ class (SOC) and preferred term (PT). These summaries will be done for: all TEAEs, all drug-related TEAEs (as determined by the investigator), and all TEAEs leading to drug discontinuation and by severity. Serious TEAEs will be summarized in the same manner.

Although a subject may have two or more TEAEs, the subject is counted only once within a System Organ Class and Preferred Term category. The same subject may contribute to two or more preferred terms in the same System Organ Class category.

Listings of subjects who have serious adverse events (SAEs) (irrespective of whether treatment emergent or not), who have study drug-related TEAE, who discontinue from study drug, and whose TEAE resulted in death, will be provided.

Adverse events reported before administration of study drug will be listed only.

Summaries of TEAEs and drug-related TEAEs will also be generated by entry diagnosis (cUTI or AP) collected by EDC, Sex (Male or Female), Race (American Indian or Alaskan Native, Asian non-Chinese, Asian Chinese, Black or African American, Native Hawaiian or Other Pacific Islander, White or Other), Age categories (< 65 years, 65 to < 75 years, and ≥ 75 years; < 65 vs ≥ 65 years; < 75 vs ≥ 75 years), Ethnicity (Hispanic/Latino, Not Hispanic/Latino), Geography (per stratification) BMI (kg/m^2) categories (<18.5 (underweight), 18.5 to <25 (normal), 25 to <30 (overweight) and ≥30 (obese)), and Baseline Creatinine Clearance groups (mL/min, as determined using the central laboratory results, or use local laboratory if results from the central laboratory are missing) using two definitions (Definition 1: <15, 15 to <30, 30 to <60, 60 to <90, or ≥90 as well as Definition 2: ≥ 140 (Augmented Renal Clearance) vs < 140).

9.4.2. Clinical Safety Laboratory Evaluations

Descriptive statistics for the mean and mean changes from baseline in clinical laboratory tests (hematology, chemistry and coagulation parameters) will be presented by study visit. If the intended numerical results are collected in the format of '<##' or '>##', the numerical part of the results will used in descriptive summary calculations, but will be presented in their original format in listings.

Potentially clinically significant (PCS) safety laboratory results will be determined based on normal limits and will be summarized by the overall worst post-baseline value using the definitions shown in Table 10, 11 and 12. For summaries of number (%) of subjects meeting PCS criteria, the subgroups of subjects in the safety population that have both a baseline and any post-baseline laboratory evaluation will be included. Subjects who met PCS criteria will be listed.

Table 10: Potential Clinical Significance (PCS) for Hematology Parameters

Laboratory Parameter	*Flag*	*Criteria**	
		Observed Value	*Change from Baseline*
Hemoglobin (g/L)	High (CH)	> 1.3 × ULN	> 30% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Hematocrit (%)	High (CH)	> 1.3 × ULN	> 30% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Erythrocyte count (RBC) (10^12/L)	High (CH)	> 1.3 × ULN	> 30% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Mean corpuscular Volume (MCV) (fL)	High (CH)	> 1.15 × ULN	> 15% Increase from Baseline
	Low (CL)	< 0.85 × LLN	> 15% Decrease from Baseline
Mean corpuscular hemoglobin (MCH) (pg)	High (CH)	> 1.15 × ULN	> 15% Increase from Baseline
	Low (CL)	< 0.85 × LLN	> 15% Decrease from Baseline
Mean corpuscular hemoglobin concentration (MCHC) (g/L)	High (CH)	> 1.15 × ULN	> 15% Increase from Baseline
	Low (CL)	< 0.85 × LLN	> 15% Decrease from Baseline
Leukocyte count (WBC) (10^9/L)	High (CH)	> 1.6 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.65 × LLN	> 60% Decrease from Baseline
Neutrophils (%)	High (CH)	> 1.6 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.65 × LLN	> 75% Decrease from Baseline
Lymphocytes(%)	High (CH)	> 1.5 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.25 × LLN	> 75% Decrease from Baseline
Eosinophils(%)	High (CH)	> 4.0 × ULN	> 300% Increase from Baseline
	Low (CL)	N/A	N/A
Monocytes(%)	High (CH)	> 4.0 × ULN	> 300% Increase from Baseline
	Low (CL)	N/A	N/A
Basophils(%)	High (CH)	> 4.0 × ULN	> 300% Increase from Baseline
	Low (CL)	N/A	N/A
Platelets (10^9/L)	High (CH)	> 1.5 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.65 × LLN	> 50% Decrease from Baseline

Notes: PCS = potentially clinically significant, ULN=upper limit of normal, LLN=lower limit of normal
CH = high PCS based on criterion value and increase from baseline.
CL = low PCS based on criterion value and decrease from baseline.
*A postdose value is considered as a PCS value if it meets both criteria for observed value and change from baseline

Table 11: Potential Clinical Significance (PCS) for Serum Chemistry Parameters

Laboratory Parameter	*Flag*	*Criteria**	
		Observed Value	*Change from Baseline*
Magnesium (mmol/L)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 65% Decrease from Baseline
Bicarbonate (mmol/L)	High (CH)	> 1.3 × ULN	> 40% Increase from Baseline
	Low (CL)	< 0.7 × LLN	> 40% Decrease from Baseline
Sodium (mmol/L)	High (CH)	> 1.05 × ULN	> 10% Increase from Baseline
	Low (CL)	< 0.90 × LLN	> 10% Decrease from Baseline
Potassium (mmol/L)	High (CH)	> 1.2 × ULN	> 20% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Phosphorus (mmol/L)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 50% Decrease from Baseline
Chloride (mmol/L)	High (CH)	> 1.2 × ULN	> 20% Increase from Baseline
	Low (CL)	< 0.8 × LLN	> 20% Decrease from Baseline
Calcium (mmol/L)	High (CH)	> 1.3 × ULN	> 30% Increase from Baseline
	Low (CL)	< 0.7 × LLN	> 30% Decrease from Baseline
Alkaline phosphatase (ALP) (U/L)	High (CH)	> 2.0 × ULN	> 100% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 80% Decrease from Baseline
Alanine Aminotransferase (ALT) (U/L)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	N/A	N/A
Aspartate Aminotransferase (AST) (U/L)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	N/A	N/A
Gamma-glutamyl transferase (U/L)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	N/A	N/A
Lactate Dehydrogenase (LDH) (U/L)	High (CH)	> 4.0 × ULN	> 300% Increase from Baseline
	Low (CL)	< 0.4 × LLN	> 60% Decrease from Baseline
Bilirubin, Total (umol/L)	High (CH)	> 2.5 × ULN	> 150% Increase from Baseline
	Low (CL)	N/A	N/A
Bilirubin, Direct (umol/L)	High (CH)	> 2.5 × ULN	> 150% Increase from Baseline
	Low (CL)	N/A	N/A
Glucose, non-fasting (mmol/L)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	< 0.6 × LLN	> 40% Decrease from Baseline
Protein, Total (g/L)	High (CH)	> 1.5 × ULN	> 50% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 50% Decrease from Baseline
Albumin (g/L)	High (CH)	> 1.5 × ULN	> 50% Increase from Baseline
	Low (CL)	< 0.5 × LLN	> 50% Decrease from Baseline
Serum creatinine (umol/L)	High (CH)	> 2.0 × ULN	> 100% Increase from Baseline
	Low (CL)	NA	NA
Blood Urea Nitrogen (BUN) (mmol/L)	High (CH)	> 3.0 × ULN	> 200% Increase from Baseline
	Low (CL)	NA	NA

Notes: PCS = potentially clinically significant, ULN=upper limit of normal, LLN=lower limit of normal
CH = high PCS based on criterion value and increase from baseline.

CL = low PCS based on criterion value and decrease from baseline.
*A postdose value is considered as a PCS value if it meets both criteria for observed value and change from baseline.

The clinical safety lab evaluations summary will be done using central laboratory results including calculated creatinine clearance shifts from baseline. The calculated creatinine clearance is based on protocol section 11.2 and rounded down to the nearest whole number. The actual weight obtained at Screening or Day 1 (baseline weight) will be used in the Cockcroft-Gault calculation throughout the study. For the calculated creatinine clearance, shifts from baseline to worst (lowest) post-baseline value will be presented using the cut-offs: <15, 15 to < 30, 30 to <60, 60 to <90, 90 to <140, and ≥ 140 (mL/min), missing values. Within each cross-tabulation the number and percent of subjects will be tabulated.

For subjects with normal liver parameters at baseline, the number and percentage of subjects with the following liver chemistry parameters will be summarized:

- ALT ≥ 3×ULN, ≥ 5×ULN, ≥ 10×ULN
- AST ≥ 3×ULN, ≥ 5×ULN, ≥ 10×ULN,
- Total bilirubin > 1.5x ULN and > 2×ULN
- Alkaline Phosphatase (ALP) ≥ 1.5×ULN and ≥ 2×ULN
- ALT ≥ 3×ULN and Total bilirubin > 1.5×ULN
- ALT ≥ 3×ULN and Total bilirubin > 2×ULN
- Potential Hy's Law cases: ALT or AST ≥ 3×ULN, Total bilirubin > 2×ULN, and ALP ≤ 2×ULN (where each individual result does not need to occur in the same blood draw)

All clinical laboratory data will be listed. Values outside the normal ranges will be flagged.

9.4.3. Coagulation Parameters

The number and percentage of subjects with PCS changes in coagulation parameters will be presented by treatment group, based on the thresholds in Table 12:

Table 12: Criteria for Potentially Clinically Significant (PCS) Coagulation Parameters

Coagulation Parameter	*Flag*	*Criteria**	
		Observed Value	*Change from Baseline*
International Normalized ratio (INR)	High (CH)	> 2.0 × ULN	> 100% increase from baseline
	Low (CL)	< 0.5x LLN	> 50% decrease from baseline
Partial thromboplastin time (PTT) (seconds)	High (CH)	> 2.0 × ULN	> 100% increase from baseline
	Low (CL)	< 0.5x LLN	> 50% decrease from baseline

Notes: PCS = potentially clinically significant
CH = high PCS based on criterion value and increase from baseline.

CL = low PCS based on criterion value and decrease from baseline.
*A postdose value is considered as a PCS value if it meets both criteria for observed value and change from baseline.

9.4.4. Vital Signs

Descriptive statistics for vital signs (heart rate, blood pressure and respiratory rate) will be presented by study visit and for the change from baseline. Descriptive statistics of maximum daily temperature will also be provided.

The number and percentage of subjects with PCS changes in vital signs will be presented by treatment group, based on the thresholds in Table 13. For summaries of number (%) of subjects meeting PCS criteria, the subgroups of subjects in the safety population that have both a baseline and any post-baseline vital sign assessment will be included.

Table 13: Criteria for Potentially Clinically Significant (PCS) Vital Signs

Vital Sign Parameter	*Flag*	*Criteria**	
		Observed Value	*Change from Baseline*
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180	Increase of ≥ 20
	Low (CL)	≤ 90	Decrease of ≥ 20
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105	Increase of ≥ 15
	Low (CL)	≤ 50	Decrease of ≥ 15
Heart Rate (bpm)	High (CH)	≥ 120	Increase of ≥ 25%
	Low (CL)	≤ 50	Decrease of ≥ 20%
Respiratory Rate (bpm)	High (CH)	≥ 20	NA
	Low (CL)	≤ 12	NA

Notes: PCS = potentially clinically significant
CH = high PCS based on criterion value and increase from baseline.
CL = low PCS based on criterion value and decrease from baseline.
mmHg = Millimeter mercury. bpm = Beat per minute.
*A postdose value is considered as a PCS value if it meets both criteria for observed value and change from baseline. Unless otherwise specified, units of measurement are given in the first column.

A listing of all vital signs will be provided by subject.

9.4.5. Electrocardiograms (ECG)

Descriptive statistics for ECG parameters will be presented by study visit and for the change from baseline.

The number and percentage of subjects with PCS changes in ECG will be presented by treatment group, based on the thresholds in Table 14. For summaries of number (%) of subjects meeting PCS criteria, the subgroups of subjects in the safety population that have both a baseline and any post-baseline ECG evaluation will be included.

Table 14: Criteria for Potentially Clinically Significant Safety ECG Values

ECG Parameter	*Flag*	*PCS Criteria*[a]	
		Observed Value	*Change from Baseline or Baseline Cut-off Value*
Heart Rate (bpm)	High (CH)	≥ 120	Increase of ≥ 25%
	Low (CL)	≤ 50	Decrease of ≥ 20%
PR Interval (msec)	High (CH)	> 200	Baseline <= 200
	Low (CL)	< 120	Baseline is >=120
QRS Interval (msec)	High (CH)	> 100	Baseline <=100
QTcB (msec)	High (CH)	> 500	Baseline ≤ 500
QTcF (msec)	High (CH)	> 450	
QTcF (msec)	High (CH)	> 480	
QTcF (msec)	High (CH)	> 500	
QTcF (msec)	High (CH)		Increase from baseline > 30
QTcF (msec)	High (CH)		Increase from baseline > 60

Notes: CH = high PCS based on criterion value and increase from baseline (or baseline cutoff value).
CL = low PCS based on criterion value and decrease from baseline.
PCS = potentially clinically significant. bpm = Beat per minute. msec = Millisecond.
[a]A postdose value is considered as a PCS value if it meets both criteria for observed value and change from baseline. Unless otherwise specified, units of measurement are given in the first column.

All ECG measurements and the overall interpretation will be listed by subject.

9.4.6. Physical Examination

Physical examination findings will be listed by subject.

9.5. Pharmacokinetic Analyses

Plasma samples from FEP-ZID-treated subjects will be analyzed to determine concentrations of FEP and ZID using a validated assay. PK analyses will be based on the PK population.

The PK parameters in Table 15 will be derived from blood samples obtained at Days 1 and 3 or 4 and summarized using descriptive statistics (mean, median, standard deviations, minimum, maximum, geometric means as well as coefficients of variation):

Table 15: Definition of PK Parameters

PK Parameter	Definition
$C_{max,8}$ µg/mL	Observed maximum concentration over the 8 hour period after the start of infusion[1]
T_{max} (h)	Time to maximum observed concentration over the 8 hour period

1: At Day 3, the summaries will be generated across all subjects irrespective of the dosing occasion selected selected for plasma sample collection.

For the purpose of pharmacokinetic analyses by this SAP, C_{max} will be directly calculated as the maximum concentration for each subject at the specific study day, and T_{max} will be calculated as the time (in hour) post- start of infusion that the Cmax was observed (time of C_{max} observed - time of start of study drug administration) rounded to the nearest minute.

Descriptive summaries of the drug concentration at each time point as well as the PK parameters will be provided for samples obtained on Days 1 and 3 or 4. Plots of concentration versus (nominal) time will be provided for individual subjects (i.e., spaghetti plots) and for the overall mean values at Day 3 or 4. Analysis of the concentration data as part of population-PK modeling methods will be described in a separate PK Analysis Plan and reported separately.

9.6. Interim Analysis

No formal interim analysis of efficacy is planned. A blinded (aggregated across treatment groups) review of the percentage of subjects in the mMITT (STIC and EUCAST IC) population will be conducted when baseline microbiologic data are available for about 60% of the randomized subjects (about 302 subjects). If the mMITT evaluability rate is lower than used in the enrollment projections or the COVID-19 pandemic results in the closure of sites and inadmissibility of participant data (see Section 9.1.1.2), the target enrollment may be increased to ensure the study is sufficiently powered.

Periodic reviews of unblinded accumulated safety data will be performed by an independent Safety Review Committee. Details are provided in Section 6.4.

10. CHANGES FROM STUDY PROTOCOL

For the pharmacokinetic analyses (Section 9.5), a clarification was added that the spaghetti plots will only be generated at Day 3 or 4.

In order to compy with differing regulatory requirements across geographic regions, two interpretive criteria (STIC and EUCAST IC) were used to determine carbapenem susceptibility, and further refinements of the definition of analyses populations (mMITT, CE and ME) using these two interpretive criteria as well as corresponding summaries were added to this SAP.

A modified-intent-to-treat-population (MITT) population, consisting of randomized subjects who received study drug, was added in this SAP in order to facilitate summaries of subjects with bacteremia (irrespective of whether the organism was also a uropathogen).

The secondary hypothesis that FEP-ZID is non inferior to meropenem based on a 10% margin was added per communications with the US FDA and the method of analyses for overall control of the Type I error was described.

11. REFERENCE

Wagenlehner FM *et al*., Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* 2015;385:1949-56.

Kaye KS, *et al*., Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. *JAMA* 2018; 319(8): 788-799.