1.0 TITLE PAGE

Protocol Title	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
Short Title	Phase 3 Study of Cefepime-zidebactam (FEP-ZID) in Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)
Protocol Number	W-5222-301
Investigational Product	Cefepime-zidebactam (FEP-ZID), also known as WCK 5222
Protocol Date	14 DEC 2021
Current Version	Global Amendment 1, version 2.0
Previous Version(s)	Original 1.0, 04 SEP 2019
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IND Number	116002
EudraCT Number	2019-002768-28

2.0 PROTOCOL APPROVAL PAGE

Protocol No.	W-5222-301
Title:	A Phase 3, Randomized, Double-blind, Multicenter, Comparative Study to Determine the Efficacy and Safety of Cefepime-zidebactam vs. Meropenem in the Treatment of cUTI or AP in Adults
IND Number	116002
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Version	Global Amendment 1, version 2.0
Date:	14 DEC 2021

Personnel Approving Protocol	**Signature**
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3.0 SYNOPSIS AND SCHEDULE OF ASSESSMENTS

Study Number	W-5222-301
Title of Study	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
Study Centers (Planned)	Approximately 50 to 60 sites, globally
Development Phase	3
Objectives	**Primary Objectives:** • 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 • To assess the overall safety and tolerability of FEP-ZID in the Safety population **Secondary Objectives**: • To evaluate the overall outcome at TOC in the Clinically Evaluable (CE) and Microbiological Evaluable (ME) populations • To evaluate the overall outcome at End-of-Treatment (EOT) in the mMITT population • To evaluate the clinical outcomes at EOT (mMITT population) and at TOC (mMITT, CE and ME populations) • To evaluate the microbiological outcome at EOT (mMITT population) and TOC (mMITT, CE and ME populations) • To evaluate the by-pathogen overall outcome (mMITT, CE and ME populations) as well as by-pathogen clinical (mMITT and CE populations) and microbiological outcomes (mMITT and ME populations) at TOC • To evaluate the clinical outcome at Late Follow-Up (LFU) in the mMITT population • To evaluate the pharmacokinetics (PK) of FEP-ZID in adult subjects with complicated urinary tract infection (cUTI) or acute pyelonephritis (AP)
Key Study Endpoints and Outcome Definitions	• ***Overall Outcome at EOT:*** o Overall Success: clinical response *and* microbiological eradication (see definitions in Section 15.2.1) o Overall Failure: clinical non-response *or* microbiological persistence (see definitions in Section15.2.1) o 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 EOT. • ***Overall Outcome at TOC:*** o Overall Success: clinical cure *and* microbiological eradication (see definitions in Section 15.2.1) o Overall Failure: clinical failure *or* microbiological persistence (see definitions in Section 15.2.1) o Overall Indeterminate: Study data are missing for evaluation of efficacy or microbiological outcome for any reason, and the subject cannot otherwise be declared an overall failure at TOC 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. • ***Clinical Outcome at EOT*** o Clinical Response (all of the following must be met): Complete resolution (or return to premorbid state) of the cUTI or AP symptoms 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); and no new

	cUTI or AP symptoms. (See Section 14.2) o Clinical Non-response (any of the following): 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 treatment-emergent adverse event (TEAE) that required discontinuation of study therapy and the cUTI or AP required additional antibiotic therapy; or death from any cause prior to the assessment (See Section 14.2). (Clinical non-response at EOT will carry forward to clinical failure at TOC.) o Clinical 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 • ***Clinical Outcome at TOC***: o Clinical Cure (all of the following must be met): Complete resolution (or return to premorbid state) of the cUTI or AP symptoms that were present at Screening; and no new cUTI or AP symptoms. (See Section 14.2) o Clinical Failure (any of the following): 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. (See Section 14.2). (A clinical non-response at the EOT visit will be carried forward as a failure to the TOC visit.) o Clinical Indeterminate: Study data are missing for evaluation of clinical cure or failure at the assessment visit for any reason. • ***Microbiological Outcome at EOT and TOC***: o Microbiological Eradication: Baseline urine culture bacterial pathogen(s) reduced to $< 10^3$ colony forming units (CFU)/mL (See Section 15.2.3) o Microbiological Persistence: Assessment urine culture grows $\geq 10^3$ CFU/mL of the baseline uropathogen at the given visit. Microbiological persistence at EOT will carry forward to TOC (See Section 15.2.3) o Microbiological Indeterminate: Unavailable follow-up urine culture or the follow-up urine culture cannot be interpreted for any reason • ***Clinical Outcome at LFU*** is detailed in Section 14.3. **Safety**: Safety evaluation is based on collection of adverse events, clinical laboratory evaluations, vital signs, and electrocardiograms (ECGs) collected during the study.
Study Design	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 of age) 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 according to an Interactive Response Technology (IRT) electronic system to receive either FEP-ZID 3 g (2 g cefepime + 1 g zidebactam) IV every eight hours (q8h) or meropenem 1 g IV q8h. Cefepime-zidebactam 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 (to maintain the study blind) 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 (Section 11.2). Subjects on hemodialysis or with CrCl < 15 mL/min at screening 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 Section 11.2. 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. Randomization will be stratified by entry diagnosis (cUTI or AP) and by geographic region. At least 30% of subjects will have a diagnosis of cUTI and at least 30% will have AP at study

	entry. Subjects who have received a single dose of an allowed short-acting antibacterial agent within 72 hours prior to randomization (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. The total duration of treatment with study drug is 7 to 10 days, including for bacteremic subjects. There is **no** oral switch therapy permitted in this study. Each subject must remain hospitalized during the study drug treatment period; no outpatient parenteral antibiotic therapy is allowed. 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 (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 performed at the Screening visit will capture the baseline cUTI/AP symptoms within 24 hours prior to 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 the 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 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 Medpace Reference Laboratory (MRL) Manual, all potential uropathogens and isolates from non-contaminated blood cultures will be sent to the central microbiology 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 four times on Day 3 (+ 1 day), as described in 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.
Inclusion Criteria	Subjects are required to meet all of the following inclusion criteria: 1. Male or female ≥ 18 years of age 2. Provide a signed written informed consent prior to any study-specific procedures 3. Meet the following clinical criteria for either cUTI or AP: A. **cUTI**: a. Have at least TWO of the following new-onset or worsening symptoms or signs: • Fever (oral, tympanic, or rectal temperature > 38°C [> 100.4°F]), which must be observed and documented by a health care provider • Nausea or vomiting • Dysuria, increased urinary frequency, or urinary urgency • Lower abdominal, suprapubic, or pelvic pain b. Have at least ONE of the following complicating factors: • Use of intermittent urethral catheterization or presence of an indwelling

urethral catheter (Note: indwelling urethral catheters that have been in place for > 24 hours prior to Screening must be removed or replaced prior to collection of the screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated)
- Current known functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder, or with a post-void residual urine volume of ≥ 100 mL
- Complete or partial obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis, urethral stricture) that is expected to be medically or surgically treated during study drug therapy (prior to EOT)
- Azotemia, defined as blood urea nitrogen (BUN) > 20 mg/dL (or blood urea > 42.8 mg/dL) or serum creatinine > 1.4 mg/dL, due to known prior intrinsic renal disease
- Documented history of urinary retention in men (e.g., previously diagnosed benign prostatic hypertrophy)

B. **AP**, defined as acute flank pain (onset within 7 days prior to randomization) or costovertebral angle (CVA) tenderness on physical examination, plus at least ONE of the following new-onset or worsening symptoms or signs:
- Fever (oral, tympanic, or rectal temperature > 38°C [> 100.4°F]), which must be observed and documented by a health care provider
- Nausea or vomiting
- Dysuria, increased urinary frequency, or urinary urgency

Note: If criteria for both cUTI and AP are met, cUTI will be considered the study entry diagnosis for randomization and analysis purposes.

4. Evidence of pyuria within 48 hours prior to randomization, as determined by an adequate midstream clean-catch urine specimen or other appropriate method that minimizes the risk of bacterial contamination with ONE of the following findings:
   - Positive leukocyte esterase on urinalysis, (where positive result is at least "++" or moderate as indicated on a urine dipstick)
   - White blood cell (WBC) count ≥ 10 cells/mm^3 in unspun urine
   - WBC count ≥ 10 cells/high-power field (HPF) in urine sediment (spun urine)

   Note: The screening/baseline urine sample (within 48 hours prior to randomization) will be submitted for culture; however, subjects may be randomized and administered study drug therapy prior to knowledge of screening/baseline urine culture results.
5. If known, the screening/baseline urine culture taken within 48 hours prior to randomization contains ≥ 10^5 colony forming unit (CFU)/mL of a Gram-negative uropathogen likely to be susceptible to meropenem
6. Expectation, in the judgment of the Investigator, that any implanted urinary instrumentation (e.g., nephrostomy tubes, ureteric stents) will be surgically removed or replaced before randomization or within 24 hours after randomization, unless removal or replacement is considered unsafe or contraindicated; note that temporary urethral catheters that have been in place for > 24 hours prior to Screening must be removed or replaced prior to collection of the Screening urine sample for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated
7. Requires hospitalization with administration of parenteral antibiotic therapy to manage the cUTI or AP in accordance with standard of care
8. All females must have a negative urine or serum pregnancy test (β –human chorionic gonadotropin [β-HCG]) at Screening AND agree to the use of one of the following highly effective methods of contraception from Screening through TOC:
   - Surgical sterilization (defined as bilateral oophorectomy or bilateral salpingectomy, but excluding bilateral tubal occlusion)
   - Post-menopausal (defined by amenorrhea for at least 24 months following cessation of all exogenous hormonal treatments)
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
   - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
   - Intrauterine device (IUD)
   - Intrauterine hormone-releasing system (IUS)
   - Sexual intercourse with only vasectomized partners, or
   - Abstinence, defined as refraining from heterosexual intercourse during the entire

	period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject All males must agree to use an acceptable barrier method of birth control (i.e., condom) with female partner(s) and must not donate sperm from Screening through TOC.
Exclusion Criteria	1. Known or suspected disease or condition that, in the opinion of the Investigator, may confound the assessment of efficacy, including but not limited to the following: • Perinephric or renal abscess • Uncomplicated lower UTI (e.g., cystitis) • Recent trauma to the pelvis or urinary tract • Polycystic kidney disease • Chronic vesicoureteral reflux • Previous or planned cystectomy or permanent urinary diversion (e.g., ileal loop, cutaneous ureterostomy) • Acute or chronic bacterial prostatitis, orchitis, or epididymitis • Concurrent non-renal source of infection (e.g., endocarditis, osteomyelitis, abscess, meningitis, pneumonia) • Previous or planned renal transplant or subject requiring hemodialysis • cUTI or AP that is known at Screening to be caused by a pathogen that is resistant to meropenem, including infection caused by fungi (e.g., candiduria) or mycobacteria (e.g., urogenital tuberculosis) 2. Receipt of potentially-effective systemic antibacterial therapy within 72 hours prior to randomization, with the exception of any of the following: • Receipt of a single dose of an allowed short-acting antibacterial agent within 72 hours prior to randomization (Appendix I). For subjects without documentation of failure on this prior therapy and/or documented uropathogen resistant to this prior therapy, this exception will be capped at a maximum of 15% of enrollment. • Receipt of > 48 hours of prior antibiotic therapy and in the Investigator's opinion, failed that prior antibiotic therapy (i.e., worsening signs and symptoms) • Documented to have cUTI or AP caused by a pathogen that is not susceptible to the prior antibiotic therapy 3. Rapidly progressive or terminal illness with a high risk of mortality due to any cause, including but not limited to acute hepatic failure, respiratory failure, or septic shock, such that the subject is unlikely to survive the study period 4. Pregnant or breastfeeding women 5. Likely to require > 10 days of antibiotic treatment to cure the current acute cUTI, or likely to receive any additional systemic antimicrobial therapy during the study period (including antibacterial, antimycobacterial, or antifungal therapy or prophylaxis) other than study drug, with the exception of (1) a single oral dose of any antifungal treatment for vaginal candidiasis, or (2) a glycopeptide (e.g., vancomycin), oxazolidinone (e.g., linezolid), or daptomycin given for a Gram-positive infection 6. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy) 7. History of epilepsy or known seizure disorder requiring current treatment with anti-seizure medication 8. Creatinine clearance < 15 mL/min or requirement for hemodialysis or CVVH 9. Current or anticipated neutropenia defined as < 500 neutrophils/mm^3, or platelet count < 50,000 per microliter 10. Screening serum total bilirubin ≥ 2 times the upper limit of normal (ULN) (unless elevated indirect bilirubin due to known Gilbert's syndrome), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 5 times ULN, or alkaline phosphatase ≥ 2 times ULN 11. History of *Clostridioides difficile*-associated disease within 6 months prior to enrolment 12. History of serious or significant hypersensitivity or allergic reaction (e.g., anaphylaxis, urticaria, other significant reaction) to any β-lactam antibiotic or to the excipient L-arginine 13. Prior receipt of FEP-ZID, prior randomization in this study, or use of any experimental drug or device within 30 days prior to enrolment 14. Unlikely to comply with the protocol (e.g., inability to return for all study visits), or any

	condition or clinically significant abnormality that, in the opinion of the Investigator, is likely to interfere with optimal study participation (e.g., evaluation of study drug efficacy, determination of safety, or completion of the expected course of treatment)
Study Visits (Calendar Days)	• Screening/Baseline Visit: Within 24 hours prior to randomization, with the exception of the urine specimen (within 48 hours prior to randomization) documenting pyuria or positive culture (if known at time of screening) • Randomization/Day 1: Day 1 is calendar day of first dose of study drug • Day 1 through Day 10: Treatment period. All subjects will receive 7 to 10 days of study drug • EOT: Last day of study drug administration (FEP-ZID or meropenem), or within 24 hours after completion of the last infusion of study drug • TOC: Day 17 ± 2 days, inclusive • LFU: Day 26 ± 2 days. The LFU assessments may be conducted via telephone contact or by another interactive technology See Schedule of Assessments for details
Investigational Medicinal Product (IMP): Test Products	FEP-ZID (Section 7.4.1): • Pharmaceutical dosage form: Intravenous infusion • Dosage: 3 g (2 g FEP + 1 g ZID) IV q8h, infused over 60 minutes (divided equally into two 30-minute infusions)
IMP: Reference Therapy	Meropenem (Section 7.4.2): • Pharmaceutical dosage form: Intravenous infusion • Dosage: 1 g IV q8h, infused over 30 minutes, followed by a 30-minute infusion of 0.9% normal saline (NS) to maintain the study blind
Study Duration	Each subject will remain in the study for approximately one month. This will include a Screening visit (within 24 hours prior to randomization), a 7-10-day treatment period starting on Day 1, and post-treatment assessments at TOC (Day 17 ± 2 days) and LFU (Day 26 ± 2 days).
Sample Size	Approximately 528 adult subjects, using a 2:1 randomization ratio (approximately 352 subjects in the FEP-ZID arm and approximately 176 in the meropenem arm), diagnosed with cUTI or AP will be enrolled in the study. Using a 15.0% non-inferiority margin, one-sided alpha of 0.025, 85% power, an overall success rate of 70% at TOC in each treatment group, 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 will be randomized (ITT population).
Statistical Methods	**Efficacy** Analysis population definitions: • Intent-to-treat (ITT) population: All subjects who were randomized, regardless of whether the subject actually received study drug • Safety population: All ITT subjects who received any amount of study drug according to the treatment actually received • Expanded microbiologically Modified Intent-To-Treat population (e-mMITT) population: All ITT subjects who received any amount of study drug and had at least one eligible uropathogen cultured from an interpretable, baseline urine sample (see Section 13.1). Sole infection with *Enterococcus* spp. and/or methicillin-resistant *Staphylococcus* spp. will exclude subjects from this population • Microbiologically Modified Intent-To-Treat population (mMITT): A subset of the e-mMITT population; subjects whose index cUTI or AP is caused by a carbapenem-resistant pathogen, solely or in combination with susceptible pathogens, will be excluded from this population • Clinically Evaluable (CE) population: All mMITT subjects who met evaluability criteria as defined in Section 18.1.5 • Microbiologically Evaluable (ME) population: Subjects who met CE population criteria, did not have a microbiological outcome at TOC of indeterminate (see Table 9), and had the microbiological determination at TOC visit within the protocol-defined window. However, any interpretable urine culture that was positive (i.e.,

	grows a study qualifying uropathogen) and was obtained at EOT through TOC will be carried forward to TOC The number and percentage of subjects in each treatment group in the mMITT population with an overall success, overall failure, and overall indeterminate outcome will be determined programmatically by treatment group for the TOC visit. For the primary efficacy analysis, the two-sided 95% confidence interval (CI) for the observed difference in the overall success rates (FEP-ZID group minus meropenem group) will be calculated using the MN score test in the mMITT analyses set. If the lower bound of the 95% CI is greater than –0.150 for the TOC visit, non-inferiority of FEP-ZID to meropenem will be concluded. In addition, if non-inferiority is declared for the primary efficacy endpoint, superiority will be evaluated using a hierarchical gatekeeping strategy for overall control of the Type I error at the one-sided 2.5% level in the e-mMITT analyses set. For selected by-subject secondary efficacy outcomes (e.g. clinical and/or microbiological outcomes at each study visit), the number and percentage of subjects in each response category will be provided by treatment group. Two-sided 95% CIs for the difference in favorable (i.e. overall success, eradication, etc.) outcome rates between the FEP-ZID and meropenem groups will be provided. For the primary analysis variable, additional analyses will also be conducted as detailed in Section 18.3.2.1.1. The by-pathogen overall (mMITT, CE and ME), clinical (mMITT and CE) and microbiological (mMITT and ME) outcomes at TOC will be summarized. Full details of all analyses will be provided in the Statistical Analysis Plan. **Safety:** Safety data will be summarized for the Safety population in which subjects are analyzed according to the treatment actually received. The number and percentage of subjects in each treatment group reporting at least one occurrence of a treatment-emergent adverse event (TEAE) or serious adverse event (SAE) for each unique Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term will be tabulated. Safety data (i.e. laboratory, vital signs and ECG parameters) will be presented by descriptive statistics of the mean and mean changes from baseline, as well as the number and percentage of subjects with potentially clinically significant (PCS) changes in safety parameters. **Pharmacokinetics (PK):** PK characterization and evaluation of plasma exposures of FEP-ZID in the PK population will be performed. Only the PK samples obtained from the FEP-ZID group will be analyzed. **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 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 for enrollment projections, the target enrolment 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 16.4.

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 (Section 14.2 and Table 4), met microbiological eradication (Section 15.2.3 and 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 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 (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 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 (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 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 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 (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.

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5.0 LIST OF TABLES

6.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AP	acute pyelonephritis
AST	aspartate aminotransferase
β-HCG	β-human chorionic gonadotropin
BL	β-lactam
BL-BLI	β-lactam/β-lactamase inhibitor
BLI	β-lactamase inhibitor
BUN	blood urea nitrogen
CBC	complete blood count
CE	Clinically Evaluable
CFU	colony-forming units
CI	confidence interval
CrCl	creatinine clearance
CRE	carbapenem-resistant *Enterobacterales*
cUTI	complicated urinary tract infection
CVA	costovertebral angle
CVVH	continuous veno-venous hemofiltration
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
e-mMITT	expanded microbiologically Modified Intent-To-Treat population
EOT	End-of-Treatment
ESBL	extended-spectrum β-lactamase
EU	European Union
FDA	Food and Drug Administration
FEP	cefepime
FEP-ZID	cefepime-zidebactam
*f*T	free time
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hERG	human ether-à-go-go-related gene
HPF	high power field
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ITT	Intent-to-treat

IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
KPC	*Klebsiella pneumoniae* carbapenemase
LFU	Late Follow-Up
MAD	multiple ascending dose
MDR	multidrug-resistant
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
mMITT	Microbiologically Modified Intent-to-treat
MN	Miettinen and Nurminen
MRL	Medpace Reference Laboratory
NOAEL	No Observed Adverse Effect Level
OXA	oxacillin-hydrolyzing β-lactamase
PCS	potentially clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PTA	probability of target attainment
SAE	serious adverse event
SI	Système International d'Unités
SRC	Safety Review Committee
TEAE	treatment-emergent adverse event
TOC	Test-of-cure
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cell
XDR	extremely drug-resistant
ZID	zidebactam

7.0 BACKGROUND AND RATIONALE

7.1 URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are a severe widespread public health problem in both community and healthcare-associated settings across the globe, a major cause of hospital admissions and are associated with important morbidity and mortality, as well as a high economic burden.

UTIs are some of the most common bacterial infections, affecting 150 million people each year worldwide (Stamm, 2001). Most UTIs are infections acquired in the community setting (57.4%), whereas 35.6% are healthcare associated and 7% are nosocomial (Al-Hasan, 2010). UTIs are an important cause of sepsis in patients admitted to hospital wards, emergency departments, and intensive care units. Urosepsis is associated with mortality of 20–40% in critically ill patients (Wagenlehner, 2008). UTI is the single most common site of hospital-acquired infection, accounting for 36% of all infections (Klevens, 2002).

Clinically, UTIs are categorized as uncomplicated or complicated. Uncomplicated UTIs typically affect individuals who are otherwise healthy and have no structural or neurological urinary tract abnormalities.

Complicated UTIs (cUTIs) are associated with factors that compromise the urinary tract or host defense, including urinary obstruction, urinary retention caused by neurological disease, immunosuppression, renal failure, renal transplantation, pregnancy and the presence of foreign bodies such as lithiasis, indwelling catheters or other drainage devices (Lichtenberger, 2008; Levison, 2013).

Pyelonephritis, a subset of cUTI, is an infection of one or both kidneys that can occur in patients without functional or anatomic abnormalities of the urinary tract (Warren, 1999). Pyelonephritis often presents with both local and systemic signs of infection including flank pain and/or tenderness, fever, and malaise. Both complicated (associated with functional alterations of the urinary tract, impaired renal function or in immunocompromised patients) and uncomplicated pyelonephritis require antibacterial treatment for a similar duration as other cUTIs. The annual incidence of pyelonephritis is estimated as 459,000 to 1,138,000 cases in the United States and 10.5 million to 25.9 million cases globally; with 20%–30% of patients requiring hospitalization (Johnson, 2018; Brown, 2005).

Urinary tract infections are caused by a range of pathogens, commonly by *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Enterobacter cloacae*, *Serratia marcescens*, *Pseudomonas aeruginosa, Enterococcus faecalis* and *Staphylococcus saprophyticus* (Mazzulli, 2012; Koeijers, 2010; Sader, 2016). Patients at particular risk to develop cUTI caused by antibiotic-resistant pathogens are those with diabetes mellitus, renal failure, paralysis, and those admitted from long-term care or rehabilitation facilities (Dunne, 2018).

7.2 UNMET MEDICAL NEED

The widespread use of broad-spectrum β-lactam (BL) antibiotics, such as 3rd-generation cephalosporins, β-lactam/β-lactamase inhibitor (BL-BLI) combinations, and carbapenems has led to the emergence and spread of multidrug-resistant (MDR) Gram-negative pathogens. The production of β-lactamase enzymes is the primary mechanism by which Gram-negative pathogens develop resistance to the BL class; such β-lactamases include Class A extended-spectrum β-lactamases (ESBLs), Class B metallo-β-lactamases, Class C AmpC β-lactamases, and Class D carbapenemases. In a recent US study on the effectiveness of empiric therapy for more than 20,000 cUTI cases diagnosed between 2015 and 2017, ESBL-positive pathogens were found in 16.8% cases (Dunne, 2018). With the increased use of carbapenems as empiric therapy for the treatment of serious Gram-negative infections, rates of carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant non-fermenting Gram-negative bacilli (e.g., *P. aeruginosa, Acinetobacter* spp.) continue to increase. These carbapenem-resistant pathogens are often extremely drug resistant (XDR, i.e., resistant to all available antibiotics except those known to be inferior in efficacy or safety) and associated with severe infections with high mortality. Thus, there is an urgent need for effective antibacterial agents that target β-lactamase-producing MDR pathogens, including carbapenemase-producing Gram-negatives, with broader therapeutic profiles compared to those of available BL-BLIs and carbapenems. The development of cefepime-zidebactam (FEP-ZID) (Section 7.3) would provide clinicians with a new treatment option for serious Gram-negative infections—including cUTI and AP—that may be amenable only to carbapenems (thereby minimizing the therapeutic-dependence on this class of antibiotics), and additionally provide coverage of certain carbapenem-resistant *Enterobacterales* expressing *Klebsiella pneumoniae* carbapenemase (KPC) and oxacillin-hydrolyzing (OXA)-48/181 β-lactamases and strains having impaired uptake of carbapenems due to porin down-regulation. In view of its unique mechanism of action and the complementary properties of its individual components, FEP-ZID is expected to provide effective treatment for infections caused by a wide variety of MDR Gram-negative pathogens, including XDR pathogens.

7.3 CEFEPIME- ZIDEBACTAM

Wockhardt Bio AG is developing FEP-ZID (also known as WCK 5222), which is a combination of cefepime hydrochloride (FEP, a 4th-generation cephalosporin) and zidebactam (ZID, also known as WCK 5107, a proprietary new chemical entity). Cefepime-zidebactam is a sterile powder blend of FEP (2 g) and ZID (1 g) for administration as an IV infusion.

Combination Product Name: FEP-ZID [cefepime hydrochloride + zidebactam] for Injection

Chemical name of FEP component: 1-[[(6R,7R)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride,72-(Z)-(O-methyloxime), monohydrochloride, monohydrate.

Chemical name of ZID component: (2S, 5R)-7-Oxo-6-sulphooxy-2-[N'-((R)-piperidin-3-carbonyl)-hydrazinocarbonyl]-1, 6-diaza-bicyclo [3.2.1] octane dihydrate.

Zidebactam is a novel bicyclo-acyl hydrazide with a unique mechanism of action as both a β-lactamase inhibitor (BLI) and a "β-lactam enhancer". Zidebactam is a broad-spectrum inhibitor of Class A and C β-lactamases. It acts as an enhancer due to its ability to selectively bind penicillin-binding protein 2 (PBP2) of *Enterobacterales, P. aeruginosa*, and *Acinetobacter* spp. with high affinity.

Distinctive features of FEP—including binding to multiple essential PBPs and relative stability towards most β-lactamases—were considered critical for the combination product of FEP-ZID. Among various penicillin and cephalosporin partners evaluated, FEP yielded the most potent in vitro activity against metallo-β-lactamase (MBL)-producing *Enterobacterales, P. aeruginosa*, and *Acinetobacter* spp.

In vitro studies revealed that FEP-ZID is active against clinical *Enterobacterales* isolates ($MIC_{50/90}$ values of 0.03/0.12 mg/L) including ESBL-expressing (0.25/1 mg/L) and plasmidic AmpC ($MIC_{50/90}$ of ≤ 0.06/≤ 0.06 mg/L) and derepressed AmpC ($MIC_{50/90}$ of 0.12/0.5 mg/L) strains (Sader, Castanheira, Huband *et al*., 2017; Sader, Rhomberg, Flamm *et al*., 2017). Cefepime-zidebactam is also active against *Klebsiella pneumoniae* carbapenemase (KPC)-producing strains of *Enterobacterales* ($MIC_{50/90}$ of 0.25/1 mg/L), as well as metallo-β-lactamase (MBL)-producing strains ($MIC_{50/90}$ of 0.5/8 mg/L) (Sader, Rhomberg, Flamm *et al*., 2017). Cefepime-zidebactam demonstrates in vitro activity against MDR *P. aeruginosa* strains ($MIC_{50/90}$ of 4/8 mg/L) including OXA- and MBL-producing (VIM and IMP) isolates, as well as isolates with overexpression of AmpC and/or efflux pump(s) (Sader, Rhomberg, Flamm *et al*., 2017). Interestingly, ZID can efficiently bind to *Acinetobacter* PBP-2 and trigger morphological transformation of bacterial cells into spheroplasts at sub-MIC concentrations. Cefepime-zidebactam exhibited moderate activity against OXA-producing *Acinetobacter baumannii* with $MIC_{50/90}$ values of 32 mg/L (Sader, Rhomberg, Flamm *et al*., 2017). Based on these in vitro observations, FEP-ZID is expected to provide effective eradication of a broad range of MDR Gram-negative pathogens harboring diverse resistance mechanisms, including MBLs.

The efficacy of FEP-ZID against common Gram-negative pathogens, including various *Enterobacterales, P. aeruginosa,* and *Acinetobacter* spp. has been demonstrated in numerous in vivo systemic infection and eradication studies, including murine thigh and lung and systemic infection. Importantly, FEP-ZID demonstrated significant efficacy against several challenging resistotypes, such as MBL-expressing *Enterobacterales* and carbapenem-resistant *P. aeruginosa* and *A. baumannii* strains. Cefepime-zidebactam in vivo efficacy against pathogens expressing CTX-M-15, SHV, TEM, CMY and KPC β-lactamases correlated well with either lower doses or a higher magnitude of eradication. These in vivo findings suggest that FEP-ZID could provide therapeutic coverage of a broad range of MDR Gram-negative pathogens.

Refer to the current FEP-ZID Investigator's Brochure for additional information regarding relevant nonclinical, microbiology, pharmacology and clinical studies.

7.3.1 Nonclinical Safety Summary

Zidebactam and FEP-ZID have undergone extensive toxicological evaluations in rat, mice, rabbit, and dog species.

The effects of ZID and FEP alone and in combination on the pulmonary, gastrointestinal and central nervous systems were investigated in male rats. The doses evaluated included FEP at 1400 mg/kg, ZID at 700 mg/kg and FEP-ZID at doses of 1400 + 350 mg/kg and 1400 + 700 mg/kg. In rats, ZID administered alone or in combination with FEP had no effect on respiratory parameters, gastrointestinal motility, motor coordination, or neurobehavioral parameters including the autonomic responses compared to the vehicle control group. The no observed effect level (NOEL) for ZID and FEP-ZID was 700 mg/kg and 1400 + 700 mg/kg, respectively.

Zidebactam was tested for hERG (human ether-à-go-go-related gene) inhibition at concentrations up to 1461 µM. The regulatory target of 50% hERG inhibition was not achieved at the highest concentration tested. The highest concentration tested is approximately 8-fold higher than the human therapeutic C_{max}. For FEP-ZID at 1- to 3-fold of the human therapeutic C_{max}, there was no inhibition of hERG current suggesting that FEP-ZID is not expected to have an effect on cardiac conduction.

A Guinea pig maximization test was carried out to assess local tolerance using the Draize score and ZID was found to be a non-irritant and non-sensitizer. Additionally, in the repeat dose toxicity studies involving 28 days of dosing, no evidence of irritation at the injection site was observed in rat or dog.

The intravenous No Observed Adverse Effect Level (NOAEL) doses, based on a 28-day repeat dose toxicity study for ZID in rat and dog are 800 and 750 mg/kg/day, respectively, and the corresponding exposure in terms of 24-hour plasma AUCs are 1948 and 1962 mg•h/L, respectively. On the basis of ZID NOAEL dose exposures in rat (800 mg/kg/day IV) and dog (750 mg/kg/day IV), a safety window of 3.5 to 4.5 times is conceivable considering the potential therapeutic ZID AUCs in the range of 450-600 mg•h/L.

The FEP-ZID combination (doses: 300 + 150 mg/kg IV and 300 + 300 mg/kg IV) was evaluated in a 4-week repeat dose toxicity study in Beagle dogs. The NOAEL of FEP-ZID in this study was determined to be 300 + 300 mg/kg/day.

Extrapolation of the dog IV NOAEL dose of 750 mg/kg to a human dose (based on body surface area) would lead to a human equivalent dose for ZID of 416 mg/kg, corresponding to 29 g for a 70 kg human. Likewise, considering the NOAEL dose (800 mg/kg) in rat, the human equivalent dose would be 64 mg/kg, corresponding to 9 g for a 70 kg human. Based on the dog IV NOAEL of FEP-ZID, the human equivalent dose would be 167 mg + 167 mg/kg, corresponding to 11 g + 11 g in a 70 kg human, which is higher than the proposed clinical dose of 6 g FEP + 3 g ZID.

Zidebactam has undergone a battery of reproductive toxicity studies. In a male and female fertility study in rats (Segment I) the doses selected were 200, 400 and 800 mg/kg. The results indicate that ZID did not cause any effects on fertility-associated parameters up to a dose of 800 mg/kg. The AUC exposure attained at NOEL (800 mg/kg) was 1650 mg•h/L (male) and 1430 mg•h/L (female).

Similarly, ZID was evaluated for teratogenic potential (Segment II) in rats and rabbits at relatively high doses and the NOAEL was found to be 800 mg/kg/day and 600 mg/kg/day, respectively. ZID attained high AUCs at NOAEL doses in rats and rabbits, 2190 and 1490 mg•h/L, respectively. In a pre- and post-natal study in rats (Segment III), ZID did not induce any reproductive system-associated changes in F0 (parents) and F1 (first generation offspring) animals. The NOAEL for post-natal, maternal and reproductive toxicity of F0 generation and pre- and post-natal development of the F1 generation was 800 mg/kg/day (corresponding to a mean C_{max} value of 899 mg/L and a mean AUC last value of 1310 mg•h/L).

In summary, the highest dose of ZID employed, provided plasma exposures (AUC) equal to or greater than 2.5-fold of human therapeutic exposures. In terms of C_{max}, the highest ZID dose tested provided 7-fold (dog) and 14-fold (rat) higher C_{max} compared with that attained in humans at the therapeutic dose. Based on the preclinical safety studies, ZID alone and in combination with FEP demonstrated a favorable safety profile.

7.3.2 Human Experience – Phase 1

Cefepime-zidebactam or ZID alone have been administered as single or repeated IV doses to 233 healthy adult (≥ 18 years) volunteers in 7 Phase 1 studies including a Single Ascending Dose (SAD) study (74 healthy volunteers), Multiple Ascending Dose (MAD) studies (33 healthy volunteers), a renal impairment study (24 healthy volunteers), a TQT study (58 healthy volunteers), an Epithelial Lining Fluid (ELF) study (36 healthy volunteers) and an Absorption, Distribution, Metabolism, and Excretion (ADME) study (8 male healthy volunteers). In addition, FEP-ZID has been administered to 24 patients with varying degrees of renal impairment (RI). The maximum IV dose of ZID administered to human was 3000 mg as a single dose (ZID alone), 4000 mg IV as a single dose with FEP (2 g), and 6000 mg per day (2000 mg every 8 hours [q8h]) as a repeated dose with FEP (2 g q8h).

The PK parameters for FEP-ZID were similar following single and multiple doses, given alone or co-administered, demonstrating lack of accumulation or PK interaction between FEP and ZID. The elimination half-life of ZID was independent of dose and ranged from approximately 1.5 to 3 hours with no observed accumulation with 8 hourly dosing, thus supporting 3 times daily administration. The PK profiles for FEP were as expected, consistent with either previous Phase 1 studies or the FEP Summary of Product Characteristics (SmPC). Urinary excretion of unchanged drug was the primary elimination pathway for both ZID and FEP. Zidebactam undergoes minimal metabolism following IV administration in humans with most (mean of approximately 90%) of the administered dose excreted unchanged in the urine. Given that FEP-ZID is primarily eliminated by renal excretion, dose adjustment is needed in subjects with moderate to severe renal impairment.

Cefepime-zidebactam and ZID alone were found to be safe and well tolerated when administered as single or multiple doses for up to 10 days. The most commonly reported TEAEs in the completed Phase 1 clinical studies included headache, diarrhea, and infusion site reactions, which were generally mild in severity and consistent with adverse drug reactions expected for treatment with this class of antibiotics. In the thorough QT study, FEP-ZID demonstrated no clinically significant QT prolongation and had no clinically significant effect on any ECG parameters in the study. Results from the renal impairment study indicate that dose adjustments will be required for subjects with renal impairment as both compounds are cleared almost entirely by renal excretion of intact drug. The intrapulmonary penetration was approximately 40% for FEP and ZID. No clinically significant changes were observed in ECGs or physical examinations across these studies. There was one report of elevated alanine aminotransferase (ALT) (179 U/L (reference range: 7-52 U/L) in one subject 3 days after receiving moxifloxacin and 5 days after receiving FEP-ZID that was considered clinically significant and resolved 8 days after onset. In addition, there was one report of *Clostridioides difficile* in one subject following multiple doses. In this subject, the toxin test for *C. difficile* was positive on the day of the TEAE, but follow-up toxin tests were negative suggesting that the *C. difficile* toxin test might not have been specific to the colitis reported in that subject. No other clinically significant laboratory changes were observed.

Refer to the current FEP-ZID Investigator's Brochure for additional information regarding relevant nonclinical, microbiology, pharmacology and clinical studies.

7.3.3 Rationale for Conducting This Study

Cefepime has been in clinical use since the mid-1990s, following its approval for the treatment of multiple indications such as cUTI and UTI, moderate-to-severe pneumonia, complicated intra-abdominal infections, and uncomplicated skin and skin structure infections, as well as empiric therapy for febrile neutropenia. Over the last 25 years, efforts to discover new BLIs for use with partner BLs have had limited success with only a few compounds demonstrating somewhat expanded β-lactamase inhibition spectrum over older BLIs. No single BLI is currently able to offer comprehensive inhibitory activity against all four classes of β-lactamases. For example, even newer BL-BLI combinations such as the recently approved ceftazidime-avibactam and meropenem-vaborbactam lack MBL pathogen coverage as well as activity against MDR *A. baumannii.* Unlike conventional BLIs that merely restore the activity of a partner BL, ZID also enhances the antibacterial activity of FEP alone. Based on the results of non-clinical and clinical Phase 1 studies of FEP-ZID and the unmet medical need, a Phase 3 study in cUTI is considered appropriate to evaluate the efficacy and safety of FEP-ZID.

Meropenem has been selected as the comparator because it has demonstrated efficacy against Gram-negative pathogens isolated in cUTIs and pyelonephritis. Meropenem has been used widely for the treatment of cUTIs, and carbapenems are the drugs of choice against ESBL-producing Gram-negative pathogens, especially in serious infections.

This is a Phase 3 study of FEP-ZID designed to evaluate the efficacy, safety, and tolerability compared with meropenem in the treatment of subjects with a cUTI or AP.

7.3.4 Benefit/Risk and Ethical Assessment

Subjects enrolled into this clinical study will have a cUTI or AP that is of sufficient severity to require hospitalization and treatment with IV antibiotics. The potential benefit to subjects participating in this study is that they will receive effective antibiotic therapy for their infection. The potential benefit of the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for cUTI and AP in the face of the changing pattern of antibiotic resistance. It is possible that FEP-ZID will not prove to be a sufficiently effective treatment for cUTI or acute pyelonephritis (i.e., not as effective as the comparator treatment). This risk is mitigated in that the subjects are closely monitored and will be managed with appropriate therapies as determined by the Investigator who is providing treatment.

The risk considerations for this study encompass the known and potential risks for the development product FEP-ZID and its component products FEP and ZID as well as the risks associated with other treatments that might be administered as described in this protocol. Other possible treatment includes the marketed product meropenem. As the risks for the marketed product are widely available in the prescribing information, such risks will not be discussed in this section.

The risks for FEP-ZID have not been fully elucidated; however, the full risk profile for FEP is described in the prescribing information for the product (refer to local FEP product labeling). Important risks as laid out in the warnings and precautions in product labeling for FEP include:

- Hypersensitivity reactions. Though subjects with hypersensitivity and serious allergic reactions to cephalosporins, carbapenems, other β-lactam antibiotics, or the excipient L-arginine are excluded from the trial, first-time episodes of such reactions could occur

- Antibiotic-associated diarrhea, *Clostridioides difficile* diarrhea, colitis, and pseudomembranous colitis. Though subjects with a history of such infections are excluded from the trial, first-time episodes of such infections could occur

- Neurotoxicity. During post-marketing surveillance, serious occurrences of encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), myoclonus, seizures, and non-convulsive status epilepticus have been reported. Most cases occurred in subjects with renal impairment who did not receive appropriate dosage adjustment and most were reversible

- Bacterial overgrowth with non-susceptible organisms

- Fall in prothrombin activity. This has been reported for many cephalosporins including FEP

- Renal impairment if high doses of aminoglycosides are administered together with cefepime. In this study, co-administration of FEP-ZID with any other antibiotic is restricted

Potential risks for FEP-ZID include the occurrence of events seen with FEP alone but that go beyond the frequency and/or severity of those seen with FEP.

Based on the current safety and efficacy profiles of FEP and ZID, it is expected that FEP-ZID could provide an effective therapeutic option for serious MDR Gram-negative infections, including those that are resistant to other β-lactam antibiotics (e.g., *Enterobacterales* expressing ESBLs, AmpC, KPC, OXA, MBL, and other β-lactamases; *P. aeruginosa* and *Acinetobacter* spp., including strains expressing β-lactamases, having porin mutations, or with efflux resistance mechanisms).

Refer to the current FEP-ZID Investigator's Brochure for additional information regarding relevant nonclinical, microbiology, pharmacology and clinical studies.

7.4 STUDY DRUG DOSE RATIONALE

In this study, study drug is defined as FEP-ZID or meropenem. The duration of therapy will be 7 to 10 days. Although the optimal duration of therapy for cUTI has not been determined, clinical practice guidelines generally recommend a minimum of 7 days of therapy; however the total recommended duration varies depending on the severity and nature of the infection as well as the chosen therapeutic agent(s) (Grabe, 2015; Gupta, 2011; Hooton, 2010). The 7 to 10-day treatment duration allowed in this study was selected to be generally consistent with clinical practice guideline recommendations as well as the duration of therapy recommended in the prescribing information for meropenem.

7.4.1 Cefepime-Zidebactam

The Sponsor undertook extensive in vivo PK/pharmacodynamic (PD) animal studies to elucidate robust PD targets for both FEP and ZID. For FEP, PD targets were determined by analyzing exposure-response for *Enterobacterales*, *P. aeruginosa* and *A. baumannii* that express clinically relevant diverse resistance mechanisms including NDM, VIM, OXA-carbapenemases and non-enzymatic resistance mechanisms such as efflux and impermeability. The unified targets were determined by co-modelling the exposure-response analysis of individual strains belonging to three pathogen groups. For *Enterobacterales*, the target was determined to be 61.4% $fT > 0.06$ x FEP-ZID minimum inhibitory concentration (MIC, determined in 1:1 ratio) for a 2 $\log_{10}$ kill. For MDR *A. baumannii*, the target was 22.4% $fT > 0.5$ x FEP-ZID MIC for a 2 $\log_{10}$ kill, and for MDR *P. aeruginosa* (including MBL producing strains), the target was 38.4% $fT > 0.03$ x FEP-ZID MIC for a 1 $\log_{10}$ kill.

Similar to FEP, ZID PD targets were also based on fractionated multiples of FEP-ZID MICs for the three pathogen groups. For a 2 $\log_{10}$ kill, the PD target for *Enterobacterales* was ~18% $fT > 0.25$ x FEP-ZID MIC, for MDR *A. baumannii*, the target was 30.7% $fT > 0.015$ x FEP-ZID MIC, and for MDR *P. aeruginosa*, the target was 34.3% $fT > 0.125$ x FEP-ZID MIC.

Employing a Population PK model using Phase 1 PK data, Monte Carlo Simulations (MCS) were undertaken to determine the probability of target attainment (PTA) for the FEP and ZID PD targets described above. The Population PK model could be best described by a two-compartment model and was developed with and without covariates. Since covariates are usually not known when initiating treatment, the model used for MCS was without covariates thereby inflating the variability in PK. MCS without covariates generally tend to provide wider confidence intervals and therefore lower PTA, which makes the PTA assessment more conservative. However, even with such a conservative model, the resulting PTA for FEP-ZID, using a clinical dose of 3 g (2 g FEP + 1 g ZID) infused over 1 hour, for *Enterobacterales*, *P. aeruginosa*, and *A. baumannii* was > 99% for organisms with FEP-ZID MICs of 64 mg/L. From a recent large surveillance study of Gram-negative pathogens, > 99% of all isolates would fall within this proposed PK/PD breakpoint.

Extensive PK modeling was done to evaluate exposure and probability of target attainment for FEP-ZID with various degrees of renal impairment and further information is provided in the Investigator's Brochure.

7.4.2 Meropenem

The comparator in this study, meropenem, is a carbapenem that is approved in the United States and Europe for the treatment various serious infections, including complicated intra-abdominal infection, bacterial meningitis, and complicated skin infection. In Europe, meropenem is also approved for cUTI at doses of 500 mg or 1 g IV q8h.

Meropenem is a preferred carbapenem over imipenem-cilastatin—the oldest available carbapenem—given the less complicated dosing in patients with renal insufficiency and improved safety profile. For example, a prospective, randomized, multicenter trial of meropenem versus imipenem-cilastatin in cUTI among hospitalized adults demonstrated that both carbapenems were associated with high and similar clinical and microbiological outcomes, however meropenem was associated with fewer drug-related AEs (8% vs. 19%) (Cox, 1995). In light of its spectrum of antimicrobial activity, its pharmacological profile, and favorable clinical and microbiological outcomes, meropenem is considered a desirable agent for the treatment of cUTI in hospitalized adults (Cox, 1995).

While the dosage of meropenem for the treatment of urinary tract infection may vary by country and clinical site (e.g., meropenem 500 mg IV q8h is an alternative regimen), an approved dosage of 1 g IV q8h infused over 30 ± 5 minutes will be administered in this Phase 3 study, followed by a 30-minute ± 5 minutes infusion of 0.9% normal saline to maintain the study blind. This dose regimen is also recommended by the European Association of Urology for the treatment of severe cases of cUTI and AP (Bonkat, 2021.

8.0 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVES

The primary objectives of this study are:

- 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

- To assess the overall safety and tolerability of FEP-ZID in the Safety population

8.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To evaluate the overall outcome at TOC in the Clinically Evaluable (CE) and Microbiological Evaluable (ME) populations

- To evaluate the overall outcome at End-of-Treatment (EOT) in the mMITT population

- To evaluate the clinical outcomes at EOT (mMITT population) and at TOC (mMITT, CE and ME populations)

- To evaluate the microbiological outcome at EOT (mMITT population), and TOC (mMITT, CE and ME populations)

- To evaluate the by-pathogen overall outcome (mMITT, CE and ME populations) as well as by-pathogen clinical (mMITT and CE populations) and microbiological outcomes (mMITT and ME populations) at TOC

- To evaluate the clinical outcome at Late Follow-Up (LFU) in the mMITT population

- To evaluate the PK of FEP-ZID in adult subjects with cUTI or AP

9.0 STUDY DESIGN

9.1 TYPE OF STUDY

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 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 (CrCl 15 to < 60 mL/min) will require dose adjustment (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 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 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 (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 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 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.

9.2 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 (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.

9.3 BLINDING AND MINIMIZATION OF BIAS

Randomization will be used to minimize the subject selection bias (Section 9.2). 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.

9.4 NUMBER OF SUBJECTS

Approximately 528 adult subjects diagnosed with cUTI or AP will be enrolled in the study. The sample size calculation is provided in Section 18.2.

9.5 EXPECTED DURATION OF SUBJECT PARTICIPATION

Each subject will remain in the study for approximately one month. This will include a Screening visit (within 24 hours prior to randomization), a treatment period (7 to 10 days) starting on Day 1 (the day that the first dose of study drug is received), and post-treatment assessments at TOC (Day 17 ± 2 days) and LFU (Day 26 ± 2 days).

10.0 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

10.1 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 who are at least 65 years old may constitute approximately 25% of randomized subjects (Wagenlehner, 2015).

10.2 INCLUSION CRITERIA

Subjects are required to meet all of the following inclusion criteria:

1. Male or female ≥ 18 years old
2. Provide a signed written informed consent prior to any study-specific procedures
3. Meet the following clinical criteria for either cUTI or AP:

A. **cUTI**:

a. Have at least TWO of the following new-onset or worsening symptoms or signs:

- Fever (oral, tympanic, or rectal temperature > 38°C [> 100.4°F]), which must be observed and documented by a health care provider
- Nausea or vomiting
- Dysuria, increased urinary frequency, or urinary urgency
- Lower abdominal, suprapubic, or pelvic pain

b. Have at least ONE of the following complicating factors:

- Use of intermittent urethral catheterization or presence of an indwelling urethral catheter (Note: indwelling urethral catheters that have been in place for > 24 hours prior to Screening must be removed or replaced prior to collection of the screening urine for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated)
- Current known functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder, or with a post-void residual urine volume of ≥ 100 mL
- Complete or partial obstructive uropathy (e.g., nephrolithiasis, tumor, fibrosis, urethral stricture) that is expected to be medically or surgically treated during study drug therapy (prior to EOT)
- Azotemia, defined as BUN > 20 mg/dL (or blood urea > 42.8 mg/dL) or serum creatinine > 1.4 mg/dL, due to known prior intrinsic renal disease
- Documented history of urinary retention in men (e.g., previously diagnosed benign prostatic hypertrophy)

B. **AP**, defined as acute flank pain (onset within 7 days prior to randomization) or costovertebral angle (CVA) tenderness on physical examination, plus at least ONE of the following new-onset or worsening symptoms or signs:

- Fever (oral, tympanic, or rectal temperature > 38°C [> 100.4°F]), which must be observed and documented by a health care provider
- Nausea or vomiting
- Dysuria, increased urinary frequency, or urinary urgency

Note: If criteria for both cUTI and AP are met, cUTI will be considered the study entry diagnosis for randomization and analysis purposes.

4. Evidence of pyuria within 48 hours prior to randomization, as determined by an adequate clean-catch urine specimen for culture or other appropriate method to collect a urine culture that minimizes risk of bacterial contamination with ONE of the following findings:
   - Positive leukocyte esterase on urinalysis, (where positive result is at least "++" or moderate as indicated on a urine dipstick)
   - WBC count ≥ 10 cells/mm^3 in unspun urine
   - WBC count ≥ 10 cells/ HPF in urine sediment (spun urine)

   Note: The screening/baseline urine sample (within 48 hours prior to randomization) will be submitted for culture; however, subjects may be randomized and administered study drug therapy prior to knowledge of screening/baseline urine culture results.
5. If known, the screening/baseline urine culture taken within 48 hours prior to randomization contains ≥ 10^5 CFU/mL of a Gram-negative uropathogen likely to be susceptible to meropenem
6. Expectation, in the judgment of the Investigator, that any implanted urinary instrumentation (e.g., nephrostomy tubes, ureteric stents) will be surgically removed or replaced before randomization or within 24 hours after randomization, unless removal or replacement is considered unsafe or contraindicated; note that temporary urethral catheters that have been in place for > 24 hours prior to Screening must be removed or replaced prior to collection of the Screening urine sample for urinalysis and culture, unless removal or replacement is considered unsafe or contraindicated
7. Requires hospitalization with administration of parenteral antibiotic therapy to manage the cUTI or AP in accordance with standard of care
8. All females must have a negative urine or serum pregnancy test (β –human chorionic gonadotropin [β-HCG]) at Screening AND agree to the use of one of the following highly effective methods of contraception from Screening through TOC:
   - Surgical sterilization (defined as bilateral oophorectomy or bilateral salpingectomy, but excluding bilateral tubal occlusion)

- Post-menopausal (defined by amenorrhea for at least 24 months following cessation of all exogenous hormonal treatments)
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Sexual intercourse with only vasectomized partners; or
- Abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

All males must agree to use an acceptable barrier method of birth control (i.e., condom) with female partner(s) and must not donate sperm from Screening through TOC.

10.3 EXCLUSION CRITERIA

1. Known or suspected disease or condition that, in the opinion of the Investigator, may confound the assessment of efficacy, including but not limited to the following:
    - Perinephric or renal abscess
    - Uncomplicated lower UTI (e.g., cystitis)
    - Recent trauma to the pelvis or urinary tract
    - Polycystic kidney disease
    - Chronic vesicoureteral reflux
    - Previous or planned cystectomy or permanent urinary diversion (e.g., ileal loop, cutaneous ureterostomy)
    - Acute or chronic bacterial prostatitis, orchitis, or epididymitis
    - Concurrent non-renal source of infection (e.g., endocarditis, osteomyelitis, abscess, meningitis, pneumonia)
    - Previous or planned renal transplant or subject requiring hemodialysis
    - cUTI or AP that is known at Screening to be caused by a pathogen that is resistant to meropenem, including infection caused by fungi (e.g., candiduria) or mycobacteria (e.g., urogenital tuberculosis)
2. Receipt of potentially-effective systemic antibacterial therapy within 72 hours prior to randomization, with the exception of any of the following:
    - Receipt of a single dose of an allowed short-acting antibacterial agent within 72 hours prior to randomization (Appendix I). For subjects without documentation of failure on this prior therapy and/or documented

uropathogen resistant to this prior therapy, this exception will be capped at a maximum of 15% of enrollment.

- Receipt of > 48 hours of prior antibiotic therapy and in the Investigator's opinion, failed that prior antibiotic therapy (i.e., worsening signs and symptoms)
- Documented to have cUTI or AP caused by a pathogen that is not susceptible to the prior antibiotic therapy

3. Rapidly progressive or terminal illness with a high risk of mortality due to any cause, including but not limited to acute hepatic failure, respiratory failure, or septic shock, such that the subject is unlikely to survive the study period
4. Pregnant or breastfeeding women
5. Likely to require > 10 days of antibiotic treatment to cure the current acute cUTI, or likely to receive any additional systemic antimicrobial therapy during the study period (including antibacterial, antimycobacterial, or antifungal therapy or prophylaxis) other than study drug, with the exception of (1) a single oral dose of any antifungal treatment for vaginal candidiasis, or (2) a glycopeptide (e.g., vancomycin), oxazolidinone (e.g., linezolid), or daptomycin given for a Gram-positive infection
6. Urinary tract surgery within 7 days prior to randomization or urinary tract surgery planned during the study period (except surgery required to relieve an obstruction or place a stent or nephrostomy)
7. History of epilepsy or known seizure disorder requiring current treatment with anti-seizure medication
8. Creatinine clearance < 15 mL/min or requirement for hemodialysis or CVVH
9. Current or anticipated neutropenia defined as < 500 neutrophils/mm^3, or platelet count < 50,000 per microliter
10. Screening serum total bilirubin ≥ 2 times the ULN (unless elevated indirect bilirubin due to known Gilbert's syndrome), or AST or ALT ≥ 5 times ULN, or alkaline phosphatase ≥ 2 times ULN
11. History of *Clostridioides difficile*-associated disease within 6 months prior to enrolment
12. History of serious or significant hypersensitivity or allergic reaction (e.g., anaphylaxis, urticaria, other significant reaction) to any β-lactam antibiotic or the excipient L-arginine
13. Prior receipt of FEP-ZID, prior randomization in this study, or use of any experimental drug or device within 30 days prior to enrolment
14. Unlikely to comply with the protocol (e.g., inability to return for all study visits), or any condition or clinically significant abnormality that, in the opinion of the Investigator, is likely to interfere with optimal study participation (e.g., evaluation of study drug efficacy, determination of safety, or completion of the expected course of treatment)

10.4 CRITERIA FOR PREMATURE DISCONTINUATION OF STUDY DRUG OR SUBJECT WITHDRAWAL FROM STUDY

Subjects should be encouraged to complete all study assessments. However, subjects may discontinue study drug or withdraw consent to participate in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled.

10.4.1 Premature Discontinuation from Study Drug Administration

Premature discontinuation of study drug administration is defined as the discontinuation of study drug before the anticipated full course of study drug required for effective treatment of a subject's infection. The minimum duration of study drug therapy is 7 days (minimum 19 doses on a q8h schedule or 13 doses on a q12h schedule). Reasons for premature discontinuation from study drug administration are recorded on the appropriate electronic case report form (eCRF) and may include, but are not limited to the following:

10.4.1.1 Discontinuations Due to Non-qualifying Baseline Urine Culture and cUTI Not Suspected

Study drug treatment should be discontinued in subjects whose baseline urine culture does not meet the requirements for a qualifying baseline urine culture (as defined in Section 13.1) and, in the opinion of the Investigator, the subject does not have a urinary tract infection.

Assessments and Procedures: Subjects who are prematurely discontinued from study drug administration will have all EOT assessments (Section 12.6) performed on the day of discontinuation. Subjects should also attend and undergo safety assessments at TOC and LFU study visits (Sections 12.7 and 12.8). If a subject is discontinued from study drug treatment on Day 3, an attempt should be made to collect any remaining PK blood samples scheduled for that day.

Clinical Outcome Assessment: For these subjects, the clinical outcome at EOT should be assessed as indeterminate.

10.4.1.2 Discontinuations Due to Safety

Possible reasons for premature discontinuation from study drug administration due to safety include, but are not limited to, the following:

- Occurrence of an AE that, in the opinion of the Investigator, warrants the subject's permanent discontinuation from study drug administration

- Hy's law criteria met, defined by at least 3-fold elevations of ALT or AST above the ULN, elevation of serum total bilirubin to > 2 times ULN without elevated serum alkaline phosphatase (≤ 2 x ULN), and no other disease or condition can be found to explain the liver test abnormalities

- Known pregnancy or breastfeeding during the study drug administration period. Female subjects whose pregnancy test is positive post-baseline must be followed through the immediate postnatal period or until termination of the pregnancy. Study center personnel must report every pregnancy as soon as possible (within 24 hours of learning of the pregnancy, as described in Section 16.1.7)

Assessments and Procedures: Subjects who are prematurely discontinued from study drug administration for safety reasons should continue to undergo study assessments (including urine culture and Daily Symptom Assessment questionnaire) at every subsequent study visit (i.e., EOT, TOC, and LFU; Sections 12.6, 12.7, and 12.8). If a subject is discontinued from study drug treatment on Day 3, an attempt should be made to collect any remaining PK blood samples scheduled for that day.

Clinical Outcome Assessment: Subjects prematurely discontinued from study drug for safety reasons and for whom further antibacterial therapy is not required for treatment of the primary infection (i.e., the cUTI or AP has resolved completely or improved to the point where no further antibacterial therapy is necessary), may be assessed by the Investigator as a clinical response at EOT (based only on the following cUTI or AP symptoms: flank pain, lower abdominal/suprapubic/pelvic pain, dysuria, urinary frequency, and/or urinary urgency). If the subject requires further antibacterial therapy for the cUTI or AP, the clinical assessment should be a clinical non-response at EOT.

10.4.1.3 Discontinuations Due to Insufficient Therapeutic Effect

Possible reasons for discontinuation from study drug due to insufficient therapeutic effect include, but are not limited to, the following:

- Clinical worsening: Subjects who show worsening of the cUTI or AP symptoms may be prematurely discontinued from study drug administration at any time. If the Investigator deems the benefit-to-risk ratio of study drug continuance acceptable, study drug administration for at least 48 hours is encouraged before discontinuation from study drug therapy

- Lack of clinical progress: For subjects who are stable, yet do not show improvement of the cUTI or AP symptoms, the Investigator is encouraged to continue study drug therapy for at least 48 hours before such subjects are considered clinical failures and prematurely discontinued from study drug therapy

Assessments and Procedures: Subjects who are prematurely discontinued from study drug due to insufficient therapeutic effect should have EOT assessments conducted (Section 12.6, including urine culture and Daily Symptom Assessment questionnaire) and undergo all assessments at TOC (Section 12.7) and LFU (Section 12.8). If a subject is discontinued from study drug treatment on Day 3, an attempt should be made to collect any remaining PK blood samples scheduled for that day. If a subject is switched to an alternative antibiotic, that therapy should be documented.

Clinical Outcome Assessment: For these subjects, the clinical outcome at EOT should be assessed as non-response.

10.4.2 Withdrawal from Study

Possible reasons for withdrawal from study include, but are not limited to, the following:

- Withdrawal of consent
- Significant subject noncompliance, defined as refusal or inability to adhere to the prescribed dosing and follow-up regimen
- Investigator determines that it is in the best interest of the subject to withdraw from the study protocol, due to reasons other than an AE

Assessments and Procedures: Subjects may withdraw from the study or be withdrawn at the request of the Investigator or Sponsor at any time. Subjects who wish to withdraw completely from this clinical study during the treatment period should be encouraged to undergo safety and efficacy assessments at the time of withdrawal. All efforts should be made to obtain a urine sample for culture and complete the Daily Symptom Assessment questionnaire. Additionally, if a subject is withdrawn on Day 3, an attempt should be made to collect any remaining PK blood samples scheduled for that day.

Clinical Outcome Assessment: These subjects should be assessed based on their response to study drug therapy at the time consent is withdrawn.

10.5 REPLACEMENT OF SUBJECTS

Randomized subjects who are withdrawn from the study will not be replaced.

10.6 STUDY TERMINATION BY SPONSOR AND TERMINATION CRITERIA

The Sponsor reserves the right to terminate an investigational site or this clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies of FEP-ZID or meropenem indicate a potential health hazard to subjects
- Serious or persistent noncompliance by the Investigators with the protocol, clinical research agreement, GCP, Form FDA 1572, or applicable regulatory guidelines in conducting the study
- Relevant ethics committee(s) or regulatory agency(ies) decision to terminate or suspend approval for the investigation or the Investigator
- Investigator request to withdraw from participation
- Subject enrolment is unsatisfactory

10.7 GUIDANCE TO INVESTIGATORS ON WHEN TO END STUDY DRUG THERAPY

The total duration of treatment of study drug is 7 to 10 days (a minimum 19 doses and a maximum 30 doses on a q8h dosing schedule for subjects with CrCl ≥ 60 mL/min throughout the study; for subjects with CrCl < 60 mL/min at any time during the study, the minimum and maximum number of doses will be adjusted according to the level and duration of renal impairment). Refer to Section 11.2 for detailed dose adjustment instructions. All EOT assessments should be completed on the last day of study drug administration, or within 24 hours after completion of the last infusion of study drug (e.g., 12-lead ECG and central laboratory assessments, as described in Section 12.6).

If additional antibacterial therapy beyond 10 days is required for the index cUTI or AP (e.g., persistent bacteremia, progressively worsening infection, or gradually improving yet persistent infection that requires additional antibacterial therapy beyond 10 days), study drug should be discontinued, and non-study antibacterial therapy should be started at the discretion of the Investigator. Administration of study drug will not be allowed beyond 10 days in any subject, including subjects with baseline bacteremia with a uropathogen. In cases of premature discontinuation of study drug, subjects should not be discontinued from the study itself; subjects should remain in the study and undergo all scheduled assessments at EOT, TOC and LFU (Section 12.6, Section 12.7, and Section 12.8).

The Investigator may use culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue study drug should be based on the clinical course rather than antimicrobial susceptibility results (***note:*** **FEP-ZID susceptibility testing will not be available at the study site**). If the index cUTI or AP is caused by a microorganism that is found (post-randomization) by the site's local microbiology laboratory to be resistant to a carbapenem (e.g., meropenem), the decision to continue or discontinue study treatment should be based on the subject's clinical course and the Investigator's clinical judgment. These cases should be discussed with the Medical Monitor before premature discontinuation of study drug, and the rationale for this decision should be recorded in the source documents.

11.0 TREATMENT OF SUBJECTS

Subjects will be randomized 2:1 to receive either FEP-ZID or meropenem. Subjects with a CrCl ≥ 60 mL/min at Screening will receive q8h IV infusions of either FEP-ZID 3 g (2 g FEP + 1 g ZID) or meropenem 1 g. Subjects with a CrCl ≥ 15 and < 60 mL/min will receive study drug infusions per Table 2 below. Cefepime-zidebactam 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 (1 g) will be infused over 30 ± 5 minutes, followed by an infusion of normal saline over 30 ± 5 minutes (to maintain the blind), for a total infusion time of 60 ± 10 minutes. The total duration of treatment is 7 to 10 days. All study drug infusions will be appropriately masked to maintain the study blind.

If a study subject has a CrCl of > 140 mL/min (calculated using the Cockcroft-Gault equation), contact the Medical Monitor to discuss the case.

11.1 STUDY DRUG

Study drug will be prepared by an unblinded pharmacist or unblinded designee with appropriate qualifications. Blinded study drugs will be labeled according to the requirements of local law and legislation, as well as current Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

11.1.1 Cefepime-Zidebactam

Subjects with CrCl ≥ 60 mL/min who are randomized to receive FEP-ZID will receive 2 consecutive infusions of 1.5 g (1 g cefepime + 0.5 g zidebactam) q8h, each IV infusion administered over 30 ± 5 minutes. Study drug regimens for subjects with renal insufficiency (CrCl 15 to 59 mL/min, inclusive) will require dose adjustment (see Table 2). Subjects with CrCl < 15 mL/min at Screening are excluded from the study.

Cefepime-zidebactam will be supplied as a sterile dry white-to-pale-yellow powder mixture of FEP 2 g and ZID 1 g (i.e., 2:1 ratio) in each vial. Cefepime-zidebactam should be stored at 2-8°C prior to use. Additional instructions for storage and reconstitution are available in the Pharmacy Manual. Information regarding the stability of FEP-ZID is presented in the Investigator's Brochure.

11.1.2 Meropenem

Subjects randomized to receive meropenem will receive 1 g IV q8h, administered over 30 ± 5 minutes and followed by an infusion of normal saline administered over 30 ± 5 minutes to maintain the blind. The meropenem infusion must always be administered as the first of the two infusions, followed by the infusion of normal saline. Meropenem requires dose adjustment for subjects with CrCl ≤ 50 mL/min (see Table 2). Subjects with CrCl < 15 mL/min at Screening are excluded from the study.

Meropenem is a white-to-pale-yellow crystalline powder packaged in vials.

Details regarding the storage, preparation, and administration of meropenem are provided in the meropenem package insert included in the Pharmacy Manual.

11.2 DOSING IN SUBJECTS WITH RENAL INSUFFICIENCY

Renal function will be estimated at Screening and daily during study drug dosing using CrCl, as estimated by the Cockcroft-Gault formula, and *rounded down* to the nearest whole number. This equation requires the use of serum creatinine levels assessed by the local laboratory.

Cockcroft-Gault formula, using serum creatinine in mg/dL and actual weight in kg:

$$\text{Males:} \quad \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females:} \quad \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

If the serum creatinine value reported is in Système International d'Unités (SI) units (i.e., µmol/L), convert to conventional units (mg/dL) using the following formula:

$$\text{Conventional units (mg/dL)} = \frac{\text{SI units (µmol/L)}}{88.4}$$

Estimated CrCl must be calculated using the Cockcroft-Gault formula every time a local laboratory assessment of serum creatinine is performed. The actual weight obtained at Screening or Day 1 will be used in the Cockcroft-Gault calculation throughout the study.

Dose adjustments based on CrCl are required for administration of FEP-ZID in subjects with a CrCl < 60 mL/min. Subjects who are treated with meropenem require a dose adjustment if their CrCl is ≤ 50 mL/min. For all subjects with CrCl between 30 and 50 mL/min, administration of study drug will be four times daily (i.e., at 0 hours, 8 hours, 12 hours, and 16 hours) in order to maintain the blind, according to Table 2. For subjects with a CrCl between 10 and 29 mL/min, administration of study drug will be twice daily as shown in Table 2. While enrolment of subjects with a CrCl of less than 15 mL/min is not allowed, a dose adjustment is provided for subjects with a CrCl between 10 and 14 mL/min in case a subject's CrCl decreases below 15 mL/min while on the study. 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 CVVH should be discontinued from study drug treatment.

All dose adjustments will be managed by the unblinded pharmacist/designee. For subjects assigned to meropenem, the active treatment must always be administered as the first infusion following randomization and the first infusion when paired with an infusion of normal saline.

Table 2: Dose Adjustments for Study Drug in Subjects with Renal Insufficiency

Time (hours)	Treatment	CrCl ≥ 60 mL/min	CrCl < 60 to > 50 mL/min	CrCl ≤ 50 to 30 mL/min	CrCl 29 to 26 mL/min	CrCl 25 to 15 mL/min	CrCl 14 to 10 mL/min+
0	FEP-ZID	2g FEP+1g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions
	Meropenem	1g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	1g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	1g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	1g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	0.5g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	0.5g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*
8	FEP-ZID	2g FEP+1g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	No infusion given	No infusion given	No infusion given
	Meropenem	1g meropenem infused over 30 minutes followed by a 30 ± 5 minute infusion of normal saline*	1g meropenem infused over 30 minutes followed by a 30 ± 5 minute infusion of normal saline*	Two infusions of normal saline, each over 30 ± 5 minutes	No infusion given	No infusion given	No infusion given
12	FEP-ZID	Not applicable	Not applicable	Single infusion of normal saline over 30 ± 5 minutes	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	Two infusions of normal saline, each over 30 ± 5 minutes
	Meropenem	Not applicable	Not applicable	1g meropenem infused over 30 ± 5 minutes	1g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	0.5g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	0.5g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*

16	FEP-ZID	2g FEP+1g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	1g FEP+0.5g ZID divided equally into two 30 ± 5 minute infusions	No infusion given	No infusion given	No infusion given
	Meropenem	1g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	1g meropenem infused over 30 ± 5 minutes followed by a 30 ± 5 minute infusion of normal saline*	Two infusions of normal saline, each over 30 ± 5 minutes	No infusion given	No infusion given	No infusion given

Abbreviations: CrCl = creatinine clearance as calculated by the Cockcroft-Gault equation; FEP –ZID = cefepime-zidebactam; g = gram.

* Note: Infusions of normal saline are performed to maintain the blind.

[+] While enrolment of subjects with a CrCl of less than 15 mL/min is not allowed, a dose adjustment is provided for CrCl of 10 to 14 mL/min in case a subject's CrCl decreases below 15 mL/min while on the study. 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 CVVH should be discontinued from study drug.

11.3 TREATMENT COMPLIANCE

Treatment compliance will be documented in the eCRF by recording the date, time (e.g., start and stop times of study drug administration), and whether or not the entire dose of study drug was administered.

11.4 PRIOR AND CONCOMITANT MEDICATIONS

11.4.1 Prior and Concomitant Systemic Antimicrobial Agents

All prior systemic antimicrobial agents (administered within 14 days prior to the date of signing the informed consent and during the Screening visit) and all systemic concomitant antimicrobial agents (administered during the study) will be documented on the eCRF.

Subjects who receive any potentially-effective systemic antibacterial therapy within 72 hours prior to randomization will be excluded from the study (Exclusion Criterion 2, Section 10.3), with these exceptions:

- Receipt of a single dose of an allowed short-acting antibacterial agent within 72 hours prior to randomization (Appendix I). For subjects without documentation of failure on this prior therapy and/or documented uropathogen resistant to this prior therapy, this exception will be capped at a maximum of 15% of enrollment.

- Receipt of > 48 hours of prior antibiotic therapy and in the Investigator's opinion, failed that prior antibiotic therapy (i.e., worsening signs and symptoms)

- Documented to have cUTI or AP caused by a pathogen that is not susceptible to the prior therapy

The concomitant use of systemic antibacterial agents with potential activity against cUTI or AP pathogens is prohibited during the study.

11.4.2 Prior and Concomitant Medications Other than Systemic Antimicrobial Agents

All other prior medications (excluding antimicrobial agents) administered within 7 days prior to and during the Screening visit and/or administered during the study will be documented on the eCRF.

Urinary anesthetics (e.g., phenazopyridine HCl) are not permitted as these agents will interfere with clinical assessments.

Simultaneous administration of meropenem with warfarin may augment its anticoagulant effects. There have been many reports of increases in the anticoagulant effects of orally administered anticoagulant agents, including warfarin, in patients who are concomitantly receiving antibacterial agents. The risk may vary with the underlying infection, age, and general status of the patient so that the contribution of the antibiotic to the increase in international normalized ratio is difficult to assess. In addition to the standard study safety laboratory assessments, frequent monitoring of the international normalized ratio should be performed during and shortly after co-administration of study therapy with an oral anticoagulant agent, as per local practice.

Probenecid interferes with the active tubular secretion of meropenem, resulting in increased plasma concentrations of meropenem. Therefore, co-administration of probenecid with meropenem is not recommended.

There is significant drug-drug interaction between meropenem and valproic acid or sodium valproate; therefore co-administration of meropenem and valproic acid or sodium valproate should be avoided.

11.5 ACCOUNTABILITY PROCEDURES

It is the responsibility of the Investigator or designee to ensure that current written records of study drug inventory and accountability are maintained. Records must be readily available for inspection by the Sponsor or Sponsor’s unblinded representative and applicable regulatory authorities at any time.

Upon receipt of study drugs, the Pharmacist or designee will acknowledge receipt via IRT, visually inspect the shipment, verify the number of FEP-ZID and meropenem vials received, document the condition of the drugs received, and store at the appropriate temperature. Refer to the Pharmacy Manual for additional information.

11.6 STUDY DRUG HANDLING AND DISPOSAL

All study drugs provided by the Sponsor should be retained at the investigational site until otherwise instructed in writing by the Sponsor. Upon completion of the study or termination of the investigational site, all unused and partially used study drugs supplied by the Sponsor may be shipped to a site designated by the Sponsor as per local regulatory requirement or destroyed on-site, following full drug accountability by the unblinded monitor. Study drug may not be returned or destroyed on-site until written permission is received from the Sponsor. Interim reconciliation and return or destruction of used vials may be arranged for high enrolling sites. Refer to the Pharmacy Manual for additional information.

12.0 STUDY PROCEDURES

The Schedule of Assessments and Procedures is located in Table 1. The terms Screening and baseline refer to the same visit or assessment. Study Day 1 is the calendar day that the subject receives the first dose of study drug; the Screening and Day 1 visits may occur on the same calendar day.

12.1 SCREENING/BASELINE VISIT

Screening visit procedures must be completed within 24 hours prior to randomization in order to determine study eligibility, with the exception of the baseline urine specimen documenting pyuria or positive culture (if known and the isolates are available to be sent to the central laboratory) which must be collected within 48 hours prior to randomization (Inclusion Criterion 4). Potential subjects who do not meet entry criteria may be re-screened as appropriate, and undergo repeat baseline assessments within 72 hours of initial screening for possible enrolment into the study.

Local or regional laboratory results will be used to determine subject eligibility for study enrolment. Any protocol-required eligibility laboratory evaluations already performed as part of the subject's regular medical care or site's standard of care within 24 h before randomization do not have to be repeated to determine subject eligibility. In addition, blood and urine samples (Table 1) must be sent to the central laboratory as part of baseline safety assessments. *If local or regional laboratory results differ clinically from the central laboratory results after randomization, the subject should not be automatically withdrawn from the study or study drug.* The subject should be assessed for safety and the Medical Monitor must be contacted to confirm if the subject is eligible to remain on study.

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

Clinical Assessments:

- Verify inclusion and exclusion criteria
- Obtain a complete medical and surgical history, including all active conditions and all relevant conditions diagnosed within the previous 5 years (no time limit for specific urological history), and demographic factors
- Record all antimicrobial medications that have been administered within 14 days and all 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
- Administer two Daily Symptom Assessment questionnaires: 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 new symptoms of the cUTI or AP within 24 hours of randomization (Appendix III)

- Record height and weight, and estimate CrCl using the Cockcroft-Gault formula (Section 11.2)

- Record vital signs of body temperature (oral, tympanic, or rectal), blood pressure, heart rate, and respiratory rate; the vital sign with the most abnormal value of the day should be recorded (if more than one is taken), and attempts should be made to measure body temperature using the same methodology throughout the study

- Perform a complete physical examination, including assessment for CVA tenderness, general appearance, skin, eyes, ears, nose, throat, lungs, heart, abdomen, urogenital, back, extremities, lymph nodes, vascular, and neurological exams

- Obtain a 12-lead ECG

- Identify, assess and record any AEs (since the time of informed consent)

Local or Regional Laboratory Assessments for Study Eligibility:

- Obtain serum transaminase (ALT, AST), total bilirubin, and alkaline phosphatase levels; serum creatinine; platelet count; absolute neutrophil count; and urinalysis (and urine microscopy if leukocyte esterase negative or only one '+' positive) to determine eligibility. If azotemia is suspected, obtain BUN (or urea)

- Obtain urinalysis (and urine microscopy if leukocyte esterase negative or only one '+' positive) to determine eligibility based on Inclusion Criterion 4 (Section 10.2). All subjects, whether cUTI or AP, must have evidence of pyuria as determined by an adequate clean-catch urine specimen for culture (or other appropriate method to collect a urine culture that minimizes the risk of bacterial contamination) with one of the following:

    - Positive leukocyte esterase on urinalysis (where positive result is at least "++" or moderate as indicated on a urine dipstick)

    - Urine WBC $\geq$ 10 cells/mm^3 in unspun urine

    - Urine WBC $\geq$ 10 cells/HPF in urine sediment

    Note that a urine specimen collected within 48 hours prior to randomization may be used to determined eligibility based on this criterion.

- Obtain serum or urine sample for pregnancy test (β-HCG) in all females and ensure that the test is negative before randomization

Central Laboratory Assessments:

- Obtain blood samples for complete blood count (CBC), chemistry panel, coagulation panel, and serum β-HCG test (if the subject is female) (Appendix II)

- Obtain a urine sample for urinalysis

Local or Regional Microbiological Assessments:

- Obtain an adequate urine specimen for urine culture and quantification; however, culture results (e.g., growth of uropathogens) are not required prior to randomization

- Obtain 2 sets of blood samples for culture (1 aerobic bottle and 1 anaerobic bottle from 2 separate venipuncture sites, for a total of 4 bottles)

12.2 STUDY DAY 1

Day 1 is the first calendar 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. The subject should receive the first dose of study drug as soon as possible following randomization. Subjects will be randomized using the IRT system after verifying that the subject meets all study inclusion criteria (Section 10.2) and no exclusion criteria (Section 10.3).

Determine the subject's creatinine clearance using the local laboratory creatinine value and administer study drug per the schedule in Sections 11.1 and 11.2.

PK Assessments:

Obtain two blood samples for PK analysis:

- Within 15 minutes after the end of infusion of the first dose of study drug (i.e. the end of administration of the second IV infusion); and

- 1 to 2 hours after the end of infusion of the 1st dose of study drug (i.e. the end of administration of the second IV infusion)

Clinical Assessments:

- Administer the Daily Symptom Assessment questionnaire (Appendix III). If Screening and Day 1 occur on the same calendar day, the Premorbid Symptom Assessment questionnaire and the Daily Symptom Assessment questionnaire should be completed prior to first dose (Section 12.1 and Appendix III) and a Daily Symptom Assessment questionnaire for Day 1 does not need to be performed

- Record one set of vital signs, including body temperature (oral, rectal, or tympanic temperature), blood pressure, heart rate and respiratory rate. For any vital sign with multiple readings on a given calendar day, the most abnormal value of the day, taken after randomization, should be recorded in the eCRF for this visit

- Perform a directed physical examination, including assessment for CVA tenderness
- Identify, assess and record any AEs
- Record any concomitant medications

12.3 STUDY DAY 2

Determine the subject's creatinine clearance using the local laboratory creatinine value and administer study drug per the schedule in Sections 11.1 and 11.2.

Clinical Assessments:

- Administer the Daily Symptom Assessment questionnaire (Appendix III)
- Record one set of vital signs, including body temperature (oral, rectal, or tympanic temperature), blood pressure, heart rate and respiratory rate. For any vital sign with multiple readings on a given calendar day, the most abnormal value of the day should be recorded in the eCRF
- Perform a directed physical examination, including assessment for CVA tenderness
- Identify, assess and record any AEs
- Record any concomitant medications

Microbiological Assessments:

- Collect 2 sets of blood samples for culture, if applicable
- Repeat urine cultures should be performed only if clinically indicated; if a subject is deemed a clinical failure, a urine specimen for culture should be obtained prior to the start of any rescue antimicrobial therapy

12.4 STUDY DAY 3

Determine the subject's creatinine clearance using the local laboratory creatinine value and administer study drug per the schedule in Sections 11.1 and 11.2.

Clinical Assessments:

- Administer the Daily Symptom Assessment questionnaire (Appendix III)
- Record one set of vital signs, including body temperature (oral, rectal, or tympanic temperature), blood pressure, heart rate and respiratory rate. For any vital sign with multiple readings on a given calendar day, the most abnormal value of the day should be recorded in the eCRF

- Perform a directed physical examination, including assessment for CVA tenderness
- Identify, assess and record any AEs
- Record any concomitant medications

Central Laboratory Assessments:

- Obtain blood and urine samples for CBC, chemistry panel, coagulation panel, and urinalysis (Appendix II)

Microbiological Assessments:

- Collect 2 sets of blood samples for culture, if applicable
- Obtain an adequate urine specimen for culture and quantification; if a subject is deemed a clinical failure, a urine specimen for culture should be obtained prior to the start of any rescue antimicrobial therapy

PK Assessments:

- Blood samples for PK analysis will be taken on Day 3 from subjects at sites where PK sampling is possible. Blood draws will be performed around one of the three study drug administrations that are convenient for plasma sample collection and processing. Blood draws for PK sampling should be taken from the arm on the **opposite side of the body** to the site of study drug infusion for **the 1 to 2 hour time point**. Samples will be taken at the following time points:
    - Immediately prior to dosing (within 30 minutes prior to the start of study drug administration)
    - 1 to 2 hours after the end of administration of study drug (i.e. the end of administration of the second IV infusion)
    - 3 to 4 hours after the end of administration of study drug (i.e. the end of administration of the second IV infusion)
    - 5 to 7 hours after the end of administration of study drug (i.e. the end of administration of the second IV infusion)
- Note: When possible, PK samples will be collected on Day 3. If it is not possible to collect PK samples on Day 3, PK samples should be collected on Day 4, at the discretion of the Investigator

12.5 STUDY DAY 4 TO EOT

Determine the subject's creatinine clearance using the local laboratory creatinine value and administer study drug per the schedule in Sections 11.1 and 11.2.

Clinical Assessments:

- Administer the Daily Symptom Assessment questionnaire (Appendix III)
- Record one set of vital signs, including body temperature (oral, rectal, or tympanic temperature), blood pressure, heart rate and respiratory rate. For any vital sign with multiple readings on a given calendar day, the most abnormal value of the day should be recorded in the eCRF
- Perform a directed physical examination, including assessment for CVA tenderness
- Identify, assess and record any AEs
- Record any concomitant medications

Microbiological Assessments:

- Repeat urine cultures should be performed only if clinically indicated; if a subject is deemed a clinical failure, a urine specimen for culture should be obtained prior to the start of any rescue antimicrobial therapy
- Collect 2 sets of blood samples for culture, if applicable

12.6 END-OF-TREATMENT (EOT)

EOT assessments are to be conducted on the day of, or within 24 hours following, the day of the last dose of study drug (between Day 7 and Day 10). Only one Daily Symptom Assessment questionnaire is required on the day of the EOT visit. The maximum duration of blinded study drug therapy is 10 days. EOT assessments should also be conducted for any premature withdrawal from study or premature discontinuation of study drug. Additional guidance on when to end study drug therapy is provided in Section 10.7.

Determine the subject's creatinine clearance using the local laboratory creatinine value and administer study drug per the schedule in Sections 11.1 and 11.2.

Clinical Assessments:

- Administer the Daily Symptom Assessment questionnaire (Appendix III)
- Record one set of vital signs, including body temperature (oral, rectal, or tympanic temperature), blood pressure, heart rate and respiratory rate. For any vital sign with multiple readings on a given calendar day, the most abnormal value of the day should be recorded in the eCRF
- Perform a complete physical examination, including assessment for CVA tenderness
- Obtain a 12-lead ECG

- Identify, assess and record any AEs
- Record any concomitant medications
- Assess the Investigator-determined clinical outcome (Section 14.2)

Central Laboratory Assessments:

- Obtain blood and urine samples for CBC, chemistry panel, coagulation panel, and urinalysis (Appendix II)

Microbiological Assessments:

- Obtain an adequate urine specimen for urine culture and quantification
- Collect 2 sets of blood samples for culture, if applicable

12.7 TEST-OF-CURE (TOC)

Perform TOC assessments on Day 17 ± 2 days.

Clinical Assessments:

- Administer the Daily Symptom Assessment questionnaire (Appendix III)
- Record vital signs, including body temperature (oral, rectal, or tympanic temperature), blood pressure, heart rate and respiratory rate. If multiple values for any vital sign are available at this visit, the most abnormal value of the day should be recorded in the eCRF
- Perform a complete physical examination, including assessment for CVA tenderness
- Obtain a 12-lead ECG only if prior study ECG(s) showed any clinically-significant abnormality
- Identify, assess and record any AEs
- Record any concomitant medications
- Assess the Investigator-determined clinical outcome (Section 14.2)

Central Laboratory Assessments:

- Obtain blood and urine samples for CBC, chemistry panel, coagulation panel, urinalysis, and serum β-HCG test (Appendix II)

Microbiological Assessments:

- Obtain an adequate urine specimen for urine culture and quantification

- Collect 2 sets of blood samples for culture, if applicable

12.8 LATE FOLLOW-UP (LFU)

The LFU visit is to be conducted on Day 26 ± 2 days. LFU assessments may be conducted via telephone contact or by another interactive technology for subjects who were considered to be a clinical cure at TOC (Section 14.2) and met microbiological eradication at TOC (Section 15.2.3 and 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.

Subjects are required to have an **in-person evaluation** if any of the following criteria are met:

- Subject missed the TOC visit
- A positive urine culture at the TOC visit
- Clinically significant laboratory or ECG abnormalities at or after the TOC visit
- New or unresolved AE(s) from a previous study visit
- Evidence suggesting recurrent or persistent UTI after the TOC visit

Clinical Assessments:

- Administer the Daily Symptom Assessment questionnaire (Appendix III)
- Obtain a 12-lead ECG only if prior ECG(s) showed any clinically-significant abnormality
- Identify, assess and record any AEs
- Record any concomitant medications
- Assess the Investigator-determined clinical outcome (Section 14.3)

Central Laboratory Assessments:

- Perform CBC, chemistry panel, coagulation panel, and/or urinalysis only if prior study laboratory results showed any clinically-significant abnormality (Appendix II); previously-normal (or abnormal but not clinically-significant) laboratory tests do not need to be repeated. **Mandatory** if the subject did not attend the TOC visit.

Microbiological Assessments:

- Collect 2 sets of blood samples for culture, if applicable
- Obtain an adequate urine specimen for urine culture and quantification

13.0 MICROBIOLOGICAL ASSESSMENTS

All microbiological cultures will be performed by the local or regional laboratory, including identification of organisms to the species level (i.e., genus and species), quantification (urine only), and preparation of clinical isolates for long term storage and shipment to the Central Microbiology Laboratory. Additional details with regard to handling and processing of microbiological specimens are provided in the MRL Laboratory Manual.

As susceptibility testing for FEP-ZID will not be available to the local or regional laboratory, FEP-ZID susceptibility results will not be available to the Investigator during real-time management of subjects. Decisions related to subject care (e.g., study drug discontinuation) will be based on the evolution of the clinical signs and symptoms of the index cUTI or AP, rather than FEP-ZID susceptibility data (see Section 10.7 for additional guidance). If susceptibility testing for meropenem is routinely performed by the local or regional laboratory using routine standard materials and methods, meropenem susceptibility test results may be used by Investigators along with clinical findings to help guide therapy in subjects whose culture results are available post-randomization.

13.1 URINE CULTURES

Urine specimens will be obtained for culture at the local or regional microbiology laboratory at the Screening, Day 3, EOT, and TOC visits, as well as at any time it is clinically indicated (Sections 12.1 to 12.5). 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 specimen for culture must be obtained from subjects who meet the criteria for an in-person visit. In addition, at any time the subject is deemed a clinical failure, a urine specimen should be obtained for culture prior to the start of any rescue antimicrobial therapy.

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

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

Urine specimens should be processed for culture by the local laboratory within 2 hours of collection. If the local laboratory cannot process the sample within 2 hours of collection, the sample may be stored at 2°C - 8°C (during transport and holding period) for up to 24 hours. If refrigeration is not possible and specimens are delayed in transport and/or processing, the urine specimen should be put into a transport tube containing preservatives, as directed in the MRL Laboratory Manual.

To be considered interpretable, the baseline urine culture must grow < 3 bacterial organisms. Organisms from interpretable urine cultures that grow ≥ 10^5 CFU/mL will be

considered potential baseline uropathogens. In addition, organisms that grow ≥ 10^3 CFU/mL and are also present in baseline blood cultures will be considered potential baseline uropathogens.

If ≥ 3 bacterial organisms are identified, the culture will be considered contaminated regardless of colony count, unless one of the isolates that grows at ≥ 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).

The list of pathogens in Table 3 may be considered causative in cUTI or pyelonephritis. Organisms identified during the study that are not listed here as uropathogens or as contaminants will be assessed on a case-by-case basis.

Table 3: Potential Uropathogens

Acinetobacter baumanni	*Klebsiella pneumoniae*
Citrobacter freundii	*Morganella morganii*
Citrobacter koseri	*Proteus mirabilis*
Corynebacterium urealyticum	*Proteus vulgaris*
Enterobacter aerogenes	*Providencia rettgeri*
Enterobacter cloacae	*Providencia stuartii*
Enterococcus faecalis	*Pseudomonas aeruginosa*
Enterococcus faecium	*Serratia marcescens*
Escherichia coli	*Staphylococcus aureus*
Klebsiella oxytoca	*Staphylococcus saprophyticus*

All organisms will be identified and quantified by the local or regional laboratory, regardless of CFU/mL. Urine cultures (screening/baseline and post-baseline) that grow ≥ 10^3 CFU/mL are to be saved for long-term storage and shipped to the central microbiology laboratory.

For the purposes of this study, the following organisms are considered "contaminants" and should not to be sent to the central microbiology laboratory:

- Non-group D streptococci (i.e., any streptococcal species with the exception of Lancefield Group D streptococci; examples of Group D streptococci include *Streptococcus bovis, S. equinus, S. alactolyticus, S. gallolyticus, S. pasteurianus, S. infantarius, S. lutetiensis*)
- Coagulase-negative staphylococci (e.g., *S. epidermidis, S. haemolyticus, S. hominis*) with the **exception** of *Staphylococcus saprophyticus,* which should be shipped to the central microbiology laboratory
- *Corynebacterium* spp. with the **exception** of *Corynebactrium urealyticum,* which should be shipped to the central microbiology laboratory
- *Lactobacillus* spp.
- *Propionibacterium* spp.
- Yeast (e.g., *Candida* spp.)

Refer to the MRL Laboratory Manual for further details, including specific procedures pertaining to the collection, processing, storage, and shipment of microbiological samples.

13.2 BLOOD CULTURES

At Screening/Baseline, 2 sets of blood samples (one aerobic blood culture bottle and one anaerobic blood culture bottle) from two separate sites must be collected for culture (i.e., 1 aerobic and 1 anaerobic bottle from 2 separate venipuncture sites, for a total of 4 bottles).

If Screening/Baseline blood culture results are positive and not considered contaminated (refer to Section 13.1 for a list of contaminants), repeat blood cultures should be obtained until the results are 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.

All organisms isolated, and not considered contaminants will be identified by the local or regional to the species level.

Refer to the MRL Laboratory Manual for further details.

13.3 CENTRAL MICROBIOLOGY LABORATORY PROCEDURES

With the exception of "contaminants" defined above (Section 13.1), isolates of all organisms from urine cultures that grow $\geq 10^3$ CFU/mL and isolates of all organisms from blood cultures collected at each visit will be shipped to the designated central microbiology laboratory. If there is an organism from a blood culture that is also grown in a contaminated urine culture at $\geq 10^3$ CFU/mL, the organism from both the urine and the blood will be shipped to the central microbiology laboratory.

The central microbiology laboratory will confirm the identity of all bacterial isolates to the species level and perform susceptibility testing against all bacterial isolates for FEP-ZID and meropenem by MIC and disk diffusions methods. Additional susceptibility testing and/or characterization using molecular testing may be performed.

Additional detail is available in the MRL Laboratory Manual.

14.0 CLINICAL EVALUATIONS

14.1 DAILY SYMPTOM ASSESSMENT QUESTIONNAIRE

During study conduct, subjects will be required to report their cUTI symptoms on a series of formal questionnaires. These will be administered by trained study center staff as described in Appendix III. The Premorbid Symptom Assessment questionnaire will be administered once at Screening/Baseline to determine if the patient normally experiences UTI symptoms (e.g. Benign Hypertrophic Prostate). The subjects will be administered the Daily Symptom Assessment questionnaire at all visits starting at Screening/Baseline Visit to capture the symptoms of their current cUTI over time (i.e. Baseline, Day 1 to EOT, TOC and LFU).

Subjects should be reminded to report any health problems directly to the Investigator. The Investigator will assess adverse events as described in Section 16.1. The Daily Symptom Assessment questionnaire is not to be used as a vehicle for AE reporting.

14.2 CLINICAL OUTCOME

The Investigator will assess the clinical outcome at EOT and TOC as described in Table 4 and Table 5 using, in part, the Daily Symptom Assessment questionnaire. The clinical outcome at EOT is defined as clinical response, non-response, or indeterminate; the clinical outcome at TOC is defined as clinical cure, clinical failure, or indeterminate. All EOT assessments should be completed on the last day of study drug administration, or within 24 hours after completion of the last infusion of study drug. Clinical non-response at EOT will carry forward to clinical failure at TOC.

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

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 as a failure.

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 as a failure.

14.3 CLINICAL OUTCOME AT LFU

For subjects who were clinically cured at the TOC visit, the Investigator will assess the clinical outcome at the LFU visit (Day 26 ± 2 days) as described in Table 6. Clinical failure at TOC, as well as an outcome of indeterminate at TOC, will carry forward to LFU.

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 symptom[1] 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.

15.0 EFFICACY ENDPOINTS

15.1 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 populations)

15.2 DERIVATION OF EFFICACY VARIABLES

15.2.1 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 (see Section 18.0).

The by-subject overall outcome is a composite outcome that is determined programmatically based on the clinical outcome (Section 15.2.2) and the microbiological outcome (Section 15.2.3) as detailed in Table 7.

Table 7: 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 9)
Overall Failure	Criteria met for clinical non-response at EOT (Table 4) or clinical failure at TOC (Table 5) OR overall microbiological persistence (Table 9). 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 shown in Table 8.

Table 8: 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 (Section 14.2 and Table 5) and by-pathogen microbiological outcome (Table 9) in a similar manner as the by-subject overall outcome.

15.2.2 Clinical Outcomes

The clinical outcome at EOT and TOC will be determined by the investigator as described in Section 14.2.

By-pathogen clinical outcome (cure, failure or indeterminate) at TOC will be determined based on the subject's clinical outcomes (Table 5) at TOC.

15.2.3 Microbiological Outcomes

A programmatic determination of by-pathogen and by-subject microbiological outcome (eradication, persistence, or indeterminate) will be made at EOT and at 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 9.

Table 9: 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 $\geq 10^3$ 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.

15.2.4 Clinical Outcome at LFU Visit

The clinical outcome at LFU (Day 26 ± 2 days) will be determined by the investigator as described in Section 14.3.

15.2.5 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 10: Emergent infections will not be considered in the determination of by-subject or by-pathogen microbiological outcomes described above.

Table 10: 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.

16.0 SAFETY EVALUATION

Subjects must be evaluated by a physician or an appropriately trained healthcare professional who is a member of the study team, at every study visit, and the evaluation must be documented. The procedures discussed below will be completed at the designated visits as outlined in Section 12.0.

16.1 ADVERSE EVENTS

16.1.1 Adverse Event Definition

An 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 (e.g. 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.

An AE does not include the following:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusion); the condition that necessitates the procedure is an AE. Any pre-existing medical condition that necessitates a procedure during the study should not be captured as an AE, and the condition should be listed in the medical history.
- Any pre-existing disease or condition or laboratory abnormality present or detected prior to the start of the study treatment regimen that does not worsen
- Laboratory abnormalities without clinical manifestations, which do not require medical intervention, or that do not result in termination or delay of study drug administration
- Situations where an untoward medical occurrence has not occurred (e.g. hospitalization for elective surgery, social and/or convenience admissions)
- Overdose of any study treatment or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation
- Progression of the index cUTI or AP or insufficient therapeutic effect of study drug, which is captured as an efficacy outcome (i.e., clinical failure at EOT or TOC); however, if progression of disease or insufficient therapeutic effect results in death, it should be recorded as a SAE (Section 16.1.5)

A TEAE is defined as an AE or SAE that occurs during or after the first administration of study drug and up through the LFU visit.

16.1.2 Relatedness to Study Drug

For each reported AE, the Investigator must make an assessment of the relationship of the event to the study drug using the following scale:

- Unrelated: The event is definitely not associated with administration of the study treatment, and is judged clearly due to causes other than the study drug treatment
- Related: The event is possibly or probably associated with administration of study treatment. Possibly-related events follow a reasonable temporal sequence from administration of study treatment, but may be due to another cause and could also be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject. Probably-related events follow a reasonable temporal sequence from administration of the study treatment, but are not easily explained by another cause such as known characteristics of the subject's clinical state or other treatment, and are confirmed by improvement after stopping the study treatment

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment.

16.1.3 Adverse Event Expectedness

An AE is considered "unexpected" if it is assessed as related to study drug and is not listed in the Reference Safety Information section of the relevant version of the IB or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. Progressive worsening of the index cUTI or AP or insufficient therapeutic effect of study drug that leads to prolonged hospitalization, re-hospitalization, or death (i.e., SAE criteria, Section 16.1.5) is considered expected—as part of potential disease progression — and not unexpected.

Some AEs are listed in the IB as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered unexpected until they have been observed with the drug under investigation.

The list of AEs included in the current version of the IB will be used as Reference Safety Information.

16.1.4 Severity Assessment

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories: mild, moderate, or severe (Table 11). This assessment is subjective and the Investigator should use medical judgment to compare the reported AE to similar types of events observed in clinical practice. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* for which specific SAE criteria are met (Section 16.1.5).

Table 11: Severity Assessments of Adverse Events.

Severity	Description
Mild	Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s)
Moderate	Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed
Severe	Symptom(s) of a sufficient severity to cause the subject severe discomfort. Severity may cause cessation of treatment with the drug. Treatment for symptom(s) or significant medical intervention is needed (if possible)
Abbreviation: AE = Adverse event.	

16.1.5 Serious Adverse Events

An SAE is any adverse experience that occurs from the signing of the informed consent to the LFU visit and that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death. Note: A life-threatening AE is an AE that, in the view of either the Investigator or Sponsor, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study treatment
- Events that jeopardize the subject sufficiently that medical or surgical intervention may be required to prevent one of the above outcomes. Examples may include, but are not limited, to:
    - Intensive treatment in an emergency room for allergic bronchospasm
    - Blood dyscrasias that do not result in hospitalization
    - Seizures that do not result in hospitalization

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained. All SAEs and follow-up information must be reported within 1 business day, or 24 hours as required by local regulations.

An SAE may qualify for expedited reporting to regulatory authorities if it is determined to be a suspected, unexpected serious adverse reaction (SUSAR). Expectedness of SAEs will be determined by the Sponsor using the Reference Safety Information specified in the IB.

The Sponsor or its designee is responsible for submitting expedited safety reports to the appropriate regulatory agency for all confirmed SUSARs. These reports will comply with the applicable regulatory requirements and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). In the case of a fatal or life-threatening SUSAR, the Sponsor or its designee will notify the appropriate regulatory agency as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. For a non-life-threatening SUSAR, the report will be submitted no later than 15 days after the Sponsor is made aware of the event.

To report an SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Clinical Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: Medpace Clinical Safety

Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-579-0444
email: medpace-safetynotification@medpace.com

Medpace SAE reporting line - EU
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
email: medpace-safetynotification@medpace.com

Supplemental information for each SAE should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded in the eCRF. All SAEs are to be followed until resolution or until the SAE is deemed stable. The Sponsor/designee may contact the study center to solicit additional information or follow up on the event.

16.1.6 Recording and Reporting Adverse Events

All AEs and SAEs will be recorded and reported from the signing of the ICF to the time of the LFU visit. The Investigator must instruct the subject to report AEs during this time period. Any death within 30 days after the last contact with the subject that the Investigator becomes aware of, needs to be reported to the Sponsor and additional information relative to the cause of death will be sought and documented.

All AEs and SAEs must be recorded in the source documents. All AEs and SAEs for subjects who have provided written informed consent will be recorded in the eCRF.

The Investigator must follow up as medically necessary on all AEs and SAEs until the events have resolved, the condition has returned to baseline, or in case of permanent impairment, until the condition stabilizes.

Any unanticipated risks to the subjects must be reported promptly to the relevant ethics committee(s) and regulatory agency(ies).

16.1.6.1 Adverse Events Based on Signs and Symptoms

Signs and symptoms can be detected during physical examination and by asking the subject the following nonspecific question: "How have you been feeling since your last visit or since you were last asked?"

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF.

16.1.6.2 Adverse Events Based on Laboratory Tests

If a new or worsening abnormal laboratory value is associated with clinical signs and symptoms, the sign or symptom or preferably an associated disease or syndrome will be reported as an AE and the associated laboratory result will be considered as additional information.

Wherever possible, the reporting Investigator should use the clinical diagnosis, rather than the laboratory value. For example, decreased hemoglobin may be diagnosed as anemia, so the diagnosis of anemia should be reported as the AE.

16.1.7 Reporting of Pregnancies Occurring During the Study

Study center personnel must report every pregnancy from the time the subject signs the ICF through the LFU Visit. Within 24 hours of learning of the pregnancy, the study center personnel must inform Medpace Clinical Safety via email. Medpace Clinical Safety will then forward the Exposure in utero (EIU) form to the study center personnel for completion. The completed form must be faxed or emailed to the SAE fax number or email provided in Section 16.1.5, even if no AE has occurred. Pregnancies in female partners of male subjects occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing the EIU Form. If the pregnancy is associated with an SAE (e.g., if the mother is hospitalized for hemorrhage), a separate SAE must be reported as described in Section 16.1.5 with the appropriate serious criterion (e.g., hospitalization) indicated, in addition to the EIU Form.

16.2 CLINICAL 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) and Section 12.0.

16.3 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:) and Section 12.0.

Unscheduled clinically-indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local or regional laboratory on an as-needed basis.

16.4 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 Sponsor will remain blinded to all data presented to, and reviewed by, the SRC.

17.0 PHARMACOKINETIC EVALUATION

The PK data acquisition and analysis strategy entails the use of a sparse PK sampling schedule. Pharmacokinetic samples will be obtained from all subjects at sites where PK sampling is possible (if not possible, sites require Sponsor's agreement in advance and in writing that PK sampling will not be performed at that site).

Pharmacokinetic sample processing and shipping procedures are described in the MRL Laboratory Manual.

17.1 PHARMACOKINETIC BLOOD SAMPLE COLLECTION

Efforts will be made to obtain PK samples from all subjects twice on Day 1 and 4 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 after the end of the infusion of the first dose of study drug (i.e. the end of administration of the second IV infusion)
    - 1 to 2 hours 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 study drug administrations that is convenient for plasma sample collection—at the following time points:
    - Within 30 minutes before starting study drug administration
    - 1 to 2 hours after the end of the infusion of study drug (i.e. the end of administration of the second IV infusion)
    - 3 to 4 hours after the end of the infusion of study drug (i.e. the end of administration of the second IV infusion)
    - 5 to 7 hours after the end of the infusion of study drug (i.e. the end of administration of the second IV infusion)

Refer to the MRL Laboratory Manual for additional details regarding PK sample collection and handling instructions.

17.2 ASSAY OF PLASMA SAMPLES

Plasma samples from FEP-ZID-treated subjects will be analyzed by a central bioanalytical laboratory to determine concentrations of FEP and ZID using a validated assay.

18.0 STATISTICAL METHODS

18.1 STUDY POPULATIONS

18.1.1 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.

18.1.2 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.

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

The expanded mMITT population will include all ITT subjects who receive any amount of study drug and have at least one eligible baseline uropathogen cultured from an interpretable baseline urine sample (see Section 13.1). Sole infection with *Enterococcus* spp. and/or methicillin-resistant *Staphylococcus* spp. will exclude subjects from this population.

18.1.4 Microbiological Modified Intent-to-Treat Population (mMITT)

A subset of the e-mMITT population; subjects whose index cUTI or AP is caused by a carbapenem-resistant pathogen, solely or in combination with susceptible pathogens, will be excluded from this population.

18.1.5 Clinically-Evaluable Population (CE)

The CE population will include all mMITT subjects who receive any amount of study drug and follow important components of the trial.

In order to be included in the CE population, 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
- Receive at least 80% of the intended doses of randomized study drug therapy (based on dates/times of first and last IV infusions)
- Receive 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
- Do not have any other major protocol deviations that may confound efficacy assessments at TOC

18.1.6 Microbiologically-Evaluable Population (ME)

The ME population will include all subjects in the CE population (Section 18.1.4) who do not have a microbiological outcome of indeterminate at TOC (see Table 9) 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.

18.1.7 Pharmacokinetic 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.

18.2 DETERMINATION OF SAMPLE SIZE

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).

18.3 METHODS OF ANALYSIS

Inferential statistical analysis of the primary efficacy endpoint will be conducted as outlined below. All data will be summarized separately by study drug (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.

18.3.1 Analysis of Disposition and Subject Characteristics

Subject disposition (enrolment, discontinuations from the study), study drug administered, premature discontinuations from study medication, withdrawals from the study, and major protocol deviations will be summarized by treatment group in the ITT, e-mMITT and mMITT populations. Reasons for exclusions from analyses sets will be tabulated.

Demographics and baseline characteristics such as diagnosis (cUTI or AP), age, sex, race, weight, relevant medal history, geographic region, clinical signs and symptoms and tallies of baseline uropathogens will be summarized by treatment group in the e-mMITT and mMITT population. Summaries of enrollment by entry diagnosis and geographic region for each treatment group in the mMITT population will be presented. Additional summaries are detailed in the Statistical Analysis Plan.

18.3.2 Efficacy Analyses

For all efficacy analyses, subject data will be analyzed in the group to which the subject was randomized.

18.3.2.1 Primary Efficacy Analyses

The primary efficacy analysis will be based on the proportion of subjects whose overall outcome is success at TOC (as defined in Section 15.2.1) in the mMITT population.

Subjects will be categorized as overall success, overall failure, or overall indeterminate. Subjects with missing data or who are lost to follow-up are defined as indeterminate for the primary analysis and are included in the denominator for the calculation of overall success rate. 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 MN. If the lower limit of the 2-sided 95% CI for the difference between treatment groups at TOC in the mMITT 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.

If non-inferiority is declared for the primary efficacy endpoint, a test for superiority will be performed using a hierarchical gatekeeping approach for overall control of the Type I error. Cefepime-zidebactam will be considered superior to meropenem at the TOC visit if the lower bound of the 2-sided 95% CI for the treatment difference in the proportion of subjects with overall success at the TOC visit in the e-mMITT population is greater than 0.00.

18.3.2.1.1 Additional Analyses of the Primary Efficacy Endpoint

Various analyses will be conducted to assess the robustness of the primary efficacy analysis.

These include:

- Analyses comparing treatment groups in terms of the difference between treatment groups in the proportion of subjects with overall success at TOC in the CE and ME populations. These are further discussed in Section 18.3.2.
- Analyses comparing 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 population where the clinical outcome is determined programmatically using the Daily Symptom Assessment questionnaire only
- Analysis conducted using the MN statistic stratified by the randomization factors: entry diagnosis (cUTI or AP) and geographical region in the mMITT population
- Assessment of the overall outcome separately across the stratification factors of geographic region and entry diagnosis (cUTI versus AP). 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 population. Other subgroup analyses may be conducted for descriptive purposes

Other sensitivity analyses of the primary efficacy outcome will be described in the Statistical Analysis Plan.

18.3.2.2 Secondary Efficacy Analyses

The secondary analysis variables are listed in Section 15.1 and their derivation described in Section 15.2. For each by-subject secondary efficacy outcome, the number and percentage of subjects with each response (e.g., for the clinical outcome at TOC response is either cure, failure or indeterminate) will be summarized by treatment group. The 2-sided 95% CI for the difference between treatment groups in the proportion of subjects with favorable response (e.g., for the clinical outcome: the difference between treatment groups in proportions of subjects with clinical cure at TOC) will be presented using the same approach as for the primary analyses. These summaries will be done for the outcomes/visits/population combinations shown below.

Table 12: Secondary Analysis Variable by Visit and Key Populations

Analysis Variable[1]	*Visit*	*Population*		
		mMITT	*CE (at TOC)*	*ME (at TOC)*
Overall Outcome	EOT	X		
	TOC	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 15.2.1, 15.2.2 and 15.2.3.
[2]: Only subjects in the mMITT population who are clinical cures at TOC will be included in the evaluations at LFU

For the by-subject microbiological outcome at TOC in the mMITT and ME 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. Likewise, the by-subject microbiological outcome at TOC will be microbiological persistence if at least one baseline uropathogen grows $\geq 10^2$ CFU/mL. Subjects with unavailable or uninterpretable urine cultures will have an indeterminate by-subject microbiological outcome at TOC.

The by-pathogen overall outcome at TOC (as described in Section 15.2.3) will be summarized in the mMITT, CE and ME populations. The by-pathogen clinical outcome will be summarized in the mMITT and CE populations and the by-pathogen microbiological outcomes at TOC will be summarized in the mMITT and ME populations. For each outcome, the number and percentage of subjects with each response category will be tabulated by treatment group and baseline uropathogen. By-subject and by-pathogen overall, clinical and microbiological outcomes at TOC for subjects with cefepime-resistant uropathogens will also be generated in the mMITT population.

The number and percentage of subjects with a superinfection and new infection will be presented by treatment group and species in the mMITT population.

Various subgroup analyses will be described in the Statistical Analyses Plan. These will include tabulation of the by-subject clinical outcome at TOC in subjects with concurrent bacteremia where the causative pathogen was also a uropathogen in the mMITT and CE populations; summaries of by-subject and by-pathogen Overall, Clinical, and Microbiological outcomes for subjects with cefepime-resistant as well as for subjects with meropenem-resistant pathogens isolated.

Other analyses as described in the Statistical Analysis Plan will also be conducted.

18.3.3 Safety Analyses

Safety will be analyzed in the Safety population (Section 18.1.2). Subjects in the Safety population will be analyzed according to the treatment actually received.

Safety will be evaluated by presenting summaries of AEs, vital signs, laboratory evaluations (hematology evaluation, chemistry panel, coagulation panel, urinalysis) and ECG parameters). 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.

Adverse events will be collected from the date/time of ICF signature through the LFU/study discharge visit. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0 or most recent) and included in data listings with both verbatim and coded/preferred term included. Adverse events occurring on or after the administration of the first dose of study drug will be considered treatment-emergent adverse events (TEAEs) (defined in Section 16.1.1).

The number and percentage of subjects in each treatment group reporting at least one occurrence of a 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 related TEAEs (as determined by the investigator), all TEAEs leading to drug discontinuation and by level of severity. The number and percentage of subjects in each treatment group reporting at least one occurrence of a treatment-emergent serious adverse event (SAE) will be tabulated by SOC and PT. Listings of TEAEs/SAEs that resulted in death will be provided.

Summaries of the number and percentages of subjects with TEAEs in subgroups defined by age, gender, BMI as well as demographic and disease characteristics will be detailed in the Statistical Analysis Plan.

Safety data (i.e. laboratory, vital signs and ECG parameters) will be presented by descriptive statistics of the mean and mean changes from baseline, as well as the number and percentage of subjects with potentially clinically significant (PCS) changes in safety parameters.

Definitions of PCS changes will be provided in the Statistical Analysis Plan for the clinical laboratory parameters, vital signs and ECGs. The critical PCS changes will be defined using a combination of values outside normal limits and unduly high or low percent change from baseline.

All safety data, including physical examination and urinalysis results, will be provided in by-subject listings.

18.3.4 Pharmacokinetic Analyses

The PK population in this study will include all subjects in the Safety population who received at least 1 dose of FEP-ZID and had at least 1 analyzable plasma PK sample (Section 18.1.6).

The following PK parameters will be derived from blood samples obtained at Day 3 and summarized using descriptive statistics (mean, median, standard deviations, minimum, maximum, geometric means as well as coefficients of variation):

Table 13: PK Parameters to be Summarized

PK Parameter	Description
$C_{max,8}$ µg/mL	Observed maximum concentration over the 8-hour period after the start of infusion
t_{max} (hours)	Time to maximum observed concentration over the 8-hour period

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. Plots of concentration versus (nominal) time will be provided for individual subjects (i.e. spaghetti plots) and for the overall mean values. In addition, analysis of the concentration data as part of population-PK modeling methods will be described in a separate PK Analysis Plan and reported separately.

18.3.5 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 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, 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 16.4.

18.4 HANDLING OF DROPOUTS AND MISSING DATA

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

Missing data 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. If no value can be obtained, imputations as detailed in the Statistical Analysis Plan will be applied
- 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
- For the primary efficacy outcome measure, subjects with missing data for either component will be considered an indeterminate response provided the subject cannot otherwise be declared a treatment failure. By definition, subjects with an indeterminate response are included in the denominator for analyses in the mMITT populations 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 population. Sensitivity analyses as described in the Statistical Analysis Plan will assess the effect of missing data on the analysis of the primary efficacy outcome
- For the clinical outcome at TOC, subjects with missing data will be considered an indeterminate response. By definition, subjects with an indeterminate response are included in the denominator for analyses based on the mMITT populations and are excluded from the CE population
- For the microbiological outcome at TOC, subjects with missing data (e.g. uninterpretable urine culture) will be considered an indeterminate response. Microbiological outcomes will not be presumed from clinical outcomes. By definition, subjects with an indeterminate response are included in the denominator for analyses based on the mMITT populations and are excluded from the ME population. Subjects with indeterminate clinical outcome are also excluded from the ME population

- Missing values for other individual data points will remain as missing, and missing data will not be imputed except as detailed in the Statistical Analysis Plan

19.0 INVESTIGATOR REQUIREMENTS

19.1 PROTOCOL ADHERENCE

Each Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor or Sponsor representative must approve any change to the protocol before seeking approval from the relevant ethics committee(s) and regulatory agency(ies). No deviation from the protocol will be permitted, except where necessary to eliminate an immediate hazard to a subject. In such cases, the deviation will be reported to the Sponsor and IEC/IRB as soon as possible. Each Investigator will be responsible for enrolling only those subjects who have met the protocol inclusion and exclusion criteria.

19.2 CASE REPORT FORMS AND OTHER ELECTRONIC SYSTEMS

Data collection will involve the use of an electronic data capture (EDC) system, to which only authorized personnel will have access. Electronic CRFs will be used to capture study data in an EDC system. Data entry into eCRFs should be handled in accordance with instructions from the Sponsor or Sponsor representative. All eCRFs must be completed by qualified study center personnel. Each Investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner.

Before the first subject is dosed at the investigational site, role-specific training will be conducted using the on-line training function within the EDC system. Once training is completed, the user will be assigned role-specific access to the EDC system. Additional study-specific EDC training may be provided during the Site Initiation Visit. The Investigator or designee will be responsible for reviewing eCRFs, resolving data queries generated via the EDC system, providing missing or corrected data, and endorsing these data within the EDC system. When prompted by the Sponsor or Sponsor representative, the Investigator will apply an electronic signature defined in the EDC system as a uniquely assigned user name and a password that together will represent a traditional handwritten signature to each eCRF.

An IRT system will be implemented for this trial which will manage study drug inventory, randomize eligible subjects and have subject treatment-assignment unblinding capabilities in an emergency. Study team personnel will receive role-specific training and individual log-in permissions before using this system.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. An electronic or certified paper copy of all completed eCRF data for that site, including query resolution correspondence, will be provided to the Investigator at the end of the study.

19.3 SOURCE DOCUMENT MAINTENANCE

All study information (including essential documents and source documents) should be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification. Study information encompasses all records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, scans and X-rays) that describe or record the methods, conduct, and/or results of the study, the factors affecting a study, and actions taken. Essential documents are those documents that individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced (e.g., source data, source documents, eCRFs, correspondence, study-related documents and materials [e.g., protocol/amendments, IB, Investigator curriculum vitae, ICFs, Pharmacy Manual, Data Management Plan, Statistical Analysis Plan, MRL Laboratory Manual, etc.]). All documents produced in this study will be maintained by the Investigator and made available for inspection by the Sponsor or Sponsor representative and applicable regulatory authorities.

If a regulatory authority notifies an Investigator of an inspection, the Investigator agrees to notify the Sponsor. If the scope of the inspection includes Study W-5222-301, the Investigator must notify the Sponsor immediately. The Investigator agrees to promptly forward to the Sponsor copies of any documentation (e.g., inspection report, audit report, Form 483) issued at the close of any regulatory authority inspection.

19.4 STUDY MONITORING REQUIREMENTS

The Sponsor or Sponsor representative will conduct study center visits to inspect study data, subjects' medical records, and eCRFs in accordance with current International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance, and the respective European Union (EU), US and local regulations and guidelines, as applicable. The Sponsor or Sponsor representative will also be able to review query status remotely, which may warrant additional communication with the Investigator and the study center's personnel. The Investigator will make available to the Sponsor, or Sponsor representative, source documents, signed ICFs, and all other study-related documents.

The Investigator will allow the Sponsor or Sponsor representative and applicable regulatory authorities to inspect facilities and records relevant to this study.

19.5 STUDY COMPLETION

The Sponsor requires the following data and materials before the study can be considered complete or terminated:

- Complete clinical and laboratory results from Screening through LFU visits for all subjects

- eCRFs properly completed by appropriate study personnel and signed and dated by the Investigator within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature

- Copies of complete study drug accountability records (e.g., study drug inventory logs and shipment and return records)

- Copies of all relevant ethics committee(s) and regulatory agency(ies) approvals and acknowledgements

- A copy of the final study status report prepared by the Investigator (an ethics committee or regulatory agency summary letter is acceptable)

20.0 PROTECTION OF HUMAN SUBJECTS AND GENERAL STUDY ADMINISTRATION

20.1 STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the current ICH E6 GCP guideline, the ethical principles of the Declaration of Helsinki, current Food and Drug Administration (FDA), EU clinical trials-related guidelines, and any additional relevant ethics committee or regulatory agency-required procedures, whichever represents the greater protection for the individual.

Investigators will apply due diligence to avoid protocol deviations. No authorized deviations or protocol waivers will be permitted. All significant protocol deviations will be recorded and reported in the clinical study report.

20.2 CONFIDENTIALITY

All study-related information received from the Sponsor, including but not limited to the W-5222 IB, protocol (and any amendments), eCRFs, study drug, and study manuals remain the sole and exclusive property of the Sponsor. This information is not to be disclosed to any party not directly associated with the study without prior written consent from the Sponsor. Investigators should take all reasonable precautions to prevent inadvertent disclosure to any party not directly associated with the study.

The Sponsor, its designee, the Investigator and all parties involved will comply with applicable subject data privacy regulations/guidance as per international and local requirements. The Investigator must assure that the privacy of the subjects, including their identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the Sponsor, subjects will be identified not by their names, but by identification code (e.g., a study-specific identification number assigned during the screening process).

Where applicable, in addition to an ICF, subjects may also be required to sign authorizations to permit the disclosure of personal health information needed for patient care and other important purposes (e.g., subjects at clinical sites in the US may sign a Health Insurance Portability and Accountability Act [HIPAA]-compliant authorization according to local IRB requirements, subjects at EU sites may sign an authorization in accordance with the General Data Protection Regulation [GDPR]). These authorizations should specify a series of administrative, physical, and technical safeguards for covered entities to use subject data and to ensure the confidentiality, integrity, and availability of electronic protected health information.

Personal medical information may be reviewed for the purpose of subject safety and/or verifying data in the source and transcribed onto the eCRF. This review may be conducted by the study monitor, authorized persons on behalf of the Sponsor, the Quality Assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

At a subject's request, medical information derived during participation in this study may be given to their personal physician or other appropriate medical personnel responsible for their welfare.

20.3 INFORMED CONSENT

This study will be conducted in compliance with the current ICH E6 GCP guideline pertaining to informed consent, the current US CFR (Title 21, Parts 50 Subparts B and D, 56 and 312) as well as relevant European and local guidelines. Subjects will give written consent to participate in the study at the first visit, before initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. The ICF must be signed and dated by the subject before study participation.

If the subject is unable to read or write, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subject is read and explained to the subject in a language understood by the subject and if the subject has consented to his participation in the study, the witness should also sign and personally date the consent form.

A copy of the signed ICF must be provided to the subject in his/her native language Signed ICFs must remain in the subjects' study files and be available for verification by the Sponsor or Sponsor representative at any time.

Subjects must be re-consented to the most current version of an IEC/IRB-approved consent form if the consent form is updated and approved during their participation in the study.

20.4 ETHICS COMMITTEE AND REGULATORY APPROVALS

The relevant ethics committee(s) and regulatory agency(ies) must approve the protocol or amended protocol (if applicable) and the corresponding ICF before the study may be initiated as per local requirements, any subject-facing materials before use, and subsequent amended protocols and corresponding ICFs, before instituting amendment-specified changes to the study, unless required for subject safety following the local legislation.

The Investigator is responsible for informing the relevant ethics committee, and potentially the local regulatory authority, of any changes made to the protocol and is to advise the relevant ethics committees and regulatory authorities, at least once a year, about the progress of the study. The Investigator (or Sponsor, if applicable) is also responsible for notifying the relevant ethics committees and regulatory authorities of any significant AEs that occur during the study according to local ethics committee requirements.

21.0 DATA HANDLING AND RECORD KEEPING

Training sessions, regular monitoring of the investigative center by the Sponsor or Sponsor representative, instruction manuals, and data verification, crosschecking, and auditing will be provided or performed to ensure quality of all study data. One or more Investigator meetings and/or Site Initiation Visits will be held to prepare the Investigator and other study personnel for appropriate collection of study data.

The Sponsor or Sponsor representative will review and validate study data as defined in the monitoring plan.

It will be the responsibility of the Investigator to ensure that the essential documents are available in the Investigator's files or at the institutional center. Any or all of these documents should be available for monitoring by the Sponsor or Sponsor representative and inspection by the regulatory authorities.

21.1 STUDY DRUG ACCOUNTABILITY

It is the responsibility of the Investigator or designee to ensure that current records of study drug inventory and accountability are maintained. Records must be readily available for inspection by the Sponsor or Sponsor's representative and open to inspection at any time by applicable regulatory authorities. Refer to Section 11.5 for more information.

21.2 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study in all formats (including, but not limited to, written, electronic, magnetic, and optical records and scans/X-rays) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or until otherwise notified in writing by the Sponsor. These records include CRFs, source documents, ICFs, regulatory documents, clinical reports and laboratory results (including, but not limited to, all local and central laboratory and microbiology results), and study drug inventory records.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of these records after the required retention period.

The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or Sponsor representative, the corresponding relevant ethics committee(s) or regulatory agency(ies). If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

The Investigator agrees by his or her participation that the results of this study may be used for submission to national or international registration. If required, these authorities will be provided with the name of the Investigator and his or her address, qualifications, and extent of involvement.

Data generated by this study must be available for inspection by applicable regulatory authorities, the Sponsor or Sponsor representative, and the relevant ethics committee(s) and regulatory agency(ies) as appropriate.

21.3 DECLARATION OF THE END OF STUDY AND CLINICAL STUDY REPORT

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

Last subject last visit is defined as completion of the LFU visit for the final subject enrolled in the study. This will be considered the end of the trial for global clinical trial submission.

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to the regulatory authority(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH Harmonised Tripartite Guideline E3: Structure and Content of Clinical Study Reports. Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. Upon completion of the clinical study report, the Sponsor will provide the Investigators with the full summary of the study results. The study results summary will also be made publicly available according to applicable EU and FDA requirements.

22.0 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control will be established by the use of written standard operating procedures (SOPs; e.g., training, monitoring, auditing, and complaint handling) to allow periodic review of the adequacy of the study activities and practices and allow for revising such practices as needed so that data and process quality are maintained, the study meets the protocol and procedural requirements, and is reproducible.

Quality assurance will be documented through independent auditing of the quality control activities, and where applicable, by regulatory authorities through inspections. Quality assurance audits may be performed during the course of the study and/or on study completion. The purpose of the audit, which is independent from routine monitoring, is to evaluate study conduct and compliance with the protocol, SOPs, GCP, and applicable regulatory requirements.

23.0 FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

24.0 PUBLICATION POLICY

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. The Sponsor will make all reasonable efforts to publish the results of the study in an appropriate peer-reviewed journal. Authorship on the primary publication of the results from this study will be based on contributions to study design, enrolment, data analysis, and interpretation of results.

25.0 REFERENCES

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26.0 APPENDICES

APPENDIX I ALLOWED AND DISALLOWED PRIOR ANTIBIOTICS

Allowed Antibiotics (One dose within 72 hours prior to randomization*)		**Disallowed Antibiotics**
Penicillins		
Amoxicillin Amoxicillin-Clavulanate Amoxicillin-Sulbactam Ampicillin Ampicillin-Sulbactam Dicloxacillin	Nafcillin Oxacillin Penicillin-G or -V Piperacillin Piperacillin-Tazobactam Ticarcillin-Clavulanate	Benzathine/Penicillin-G Procaine
Cephalosporins		
Cefaclor Cefadroxil Cefazolin Cefdinir Cefepime Cefiderocol Cefixime (200 mg) Cefditoren Cefoperazone (with or without sulbactam) Cefotaxime Ceftolozane-tazobactam	Cefpodoxime Cefprozil Ceftaroline Loracarbef Ceftibuten Cefuroxime Cephalexin Ceftazidime (with or without avibactam)	Cefixime (400 mg) Ceftriaxone
Carbapenems		
Doripenem Imipenem Meropenem		Ertapenem Meropenem-vaborbactam
Glycopeptides		
Televancin Vancomycin		Dalbavancin Oritavancin
Fluoroquinolones		
Ciprofloxacin Norfloxacin	Ofloxacin Pefloxacin	Levofloxacin Moxifloxacin Prulifloxacin
Macrolides		
Clarithromycin Erythromycin		Azithromycin Clarithromycin XL
Tetracyclines		
Doxycycline (100 mg) Minocycline		Doxycycline (200 mg) Minocycline Extended Release Tigecycline
Oxazolidinones		
Linezolid		Tedizolid

Allowed Antibiotics (One dose within 72 hours prior to randomization*)		**Disallowed Antibiotics**
Miscellaneous		
Clindamycin Metronidazole Pipemidic acid Trimethoprim-sulfamethoxazole/Co-trimoxazole	Nitrofurantoin Nalidixic acid Amikacin Gentamicin	Fosfomycin (IV and oral) Plazomicin

*Prior (within 72 hours prior to randomization) administration of potentially effective systemic antibacterial therapy is an Exclusion Criterion (Section 10.3); however, subjects may be eligible for the study despite prior antimicrobial therapy if they received a single dose of an allowed short-acting antibacterial agent within 72 hours prior to randomization. For subjects without documentation of failure on this prior therapy and/or documented uropathogen resistant to this prior therapy, this exception will be capped at a maximum of 15% of enrollment.

For the purposes of this protocol, short-acting is defined as having a dosage frequency of more than once a day. If a subject received a prior short-acting systemic antibiotic that is not listed here, the Investigator must contact the Medical Monitor to ensure subject eligibility.

APPENDIX II SAFETY LABORATORY TESTS CONDUCTED BY THE CENTRAL LABORATORY

Hematology:	**Chemistry (Serum Concentrations):**
• Hemoglobin • Hematocrit • Erythrocyte count • Mean red blood cell volume • Mean red blood cell hemoglobin • Mean red blood cell hemoglobin concentration • Leukocyte count (WBC) • Neutrophils (including immature neutrophils [bands] and absolute neutrophil count) • Lymphocytes • Monocytes • Eosinophils • Basophils • Platelets **Coagulation:** • Prothrombin time/International normalized ratio (PT/INR) • Partial thromboplastin time **Urinalysis:** • Specific gravity • pH • Protein • Glucose • Ketones • Bilirubin • Occult blood • Nitrites • Urobilinogen • Leukocyte esterase	• Glucose • Calcium • Albumin • Total protein • Sodium • Potassium • Carbon dioxide • Chloride • Blood urea nitrogen (BUN) • Creatinine • Alkaline phosphatase • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Total and direct bilirubin • Magnesium • Lactate dehydrogenase (LDH) • Phosphorus • Gamma-glutamyl transferase (GGT) • β-Human chorionic gonadotropin (β-HCG) for females

APPENDIX III STUDY W-5222-301 PREMORBID AND DAILY SYMPTOM ASSESSMENT QUESTIONNAIRES

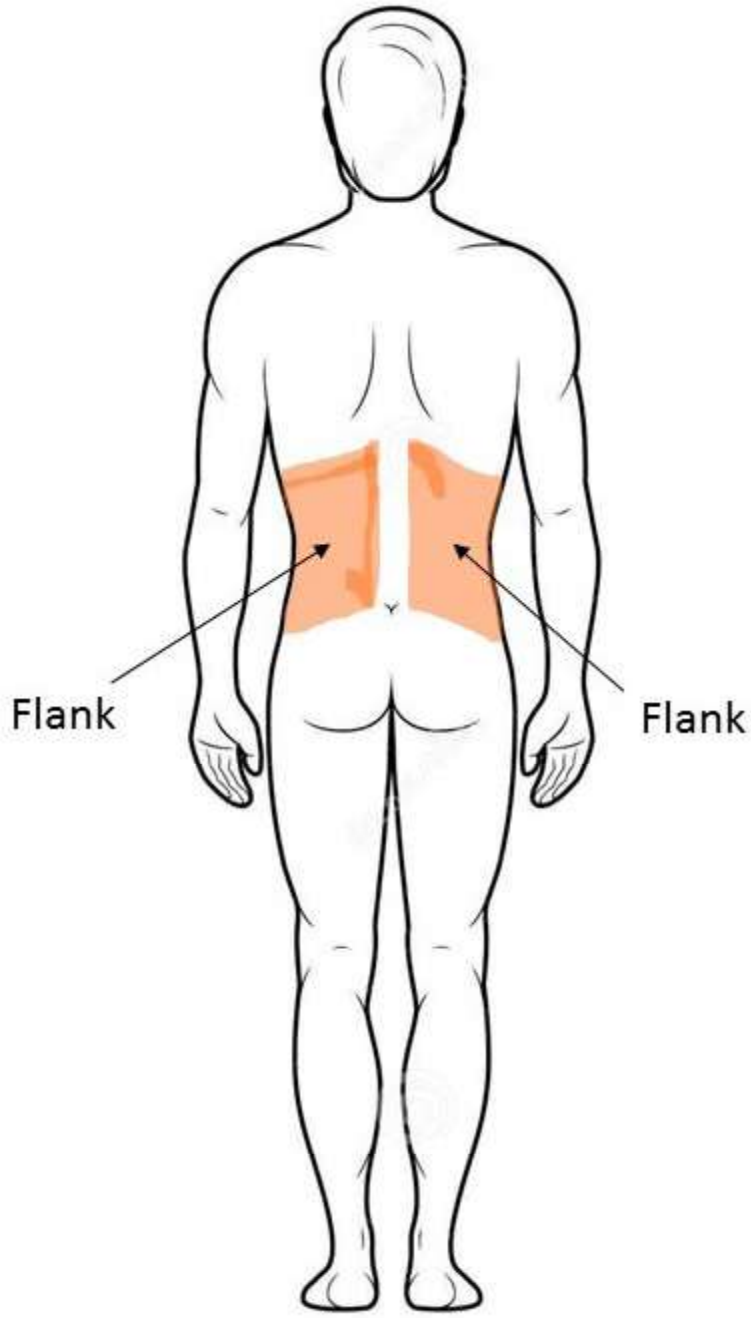
Interviewer Instructions for Premorbid and Daily Symptom Assessment Questionnaire

Interviewers must complete the symptom assessment training prior to administering the Premorbid or Daily Symptom Assessment questionnaires to any study subject. Training will take place at the Site Initiation Visit. A standardized procedure for the administration of the two types of Symptom Assessment questionnaires will be applied at every site to minimize bias. To ensure standardization, please read and follow these instructions carefully before administering the questionnaire:

- The questionnaire should be completed prior to other examinations, before substantial encounters with professional healthcare providers occur (e.g., before exchange of clinical information such as disease status occurs).
- Administer the questionnaire in a quiet place where the subject can be interviewed alone, without interference from family or study staff members.
- Enter the symptom assessment date and time. ***NOTE*:** At the Screening Visit, **two** questionnaires are required: the Premorbid Symptom Assessment Questionnaire (which records symptoms **prior** to the onset of current cUTI or AP) and the Daily Symptom Assessment questionnaire to assess new symptoms of the cUTI or AP within 24 hours of randomization.
- Read all instructions verbatim and aloud. Note there are separate instructions for the Premorbid Symptom Assessment Questionnaire and the Daily Symptom Assessment questionnaire to be performed at all other visits (page 1 of questionnaire).
- Read all questions and each response option verbatim and aloud (e.g., “Pain or burning during urination: No symptoms, mild symptoms, moderate symptoms, or severe symptoms?”). Instruct the subject to choose only ONE response for each item and record the response selected by the subject. Definitions of mild, moderate, and severe follow the severity assessments for AEs provided in Table 11, namely:
    - Mild: Symptom barely noticeable to the subject or does not make the subject uncomfortable; it does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of the symptom.
    - Moderate: Symptom of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of the symptom may be needed.
    - Severe: Symptom of a sufficient severity to cause the subject severe discomfort. Treatment for the symptom is needed.
- Show the anatomical diagram of the flank to the subject when reading the question about flank pain.
- The instructions, questions and response options may be repeated at the request of the subject.

- Do not interpret the questions for the subject or comment on their responses.

Please show this anatomical diagram of the flank to the subject when reading the question about flank pain:



STUDY W-5222-301 PREMORBID SYMPTOM ASSESSMENT QUESTIONNAIRE

[Page 1 of 2]

Instructions for the 1st Questionnaire to be administered at the Screening Visit to Capture Premorbid Symptoms (*read aloud to the subject*):

"This questionnaire asks about symptoms you might have experienced before the start of your current urinary tract infection. Some symptoms can be caused by health problems other than urinary tract infection; therefore, we want to know what symptoms you experience, if any, when you do not have a urinary tract infection.

Please respond whether you have had any of the following symptoms in the 14 days before your current urinary tract infection started and how severe those symptoms were. Answer each question by choosing only one response from the following possible options: No symptoms, mild symptoms, moderate symptoms, or severe symptoms. When answering these questions don't think about how you feel now; think about how you felt before the start of your current urinary tract infection."

STUDY W-5222-301 PREMORBID SYMPTOM ASSESSMENT QUESTIONNAIRE

[Page 2 of 2]

Site:	
Subject Number:	
Visit:	Screening/Baseline
Date (DD/MM/YYYY):	
Assessment Time (24-h Clock):	

Symptom Assessment	No Symptom	Mild	Moderate	Severe
1. Lower back or flank pain (Please show the figure indicating the flank area to the subject)	☐	☐	☐	☐
2. Pain or uncomfortable pressure in the lower abdomen or pelvic area	☐	☐	☐	☐
3. Pain or burning during urination	☐	☐	☐	☐
4. Frequent urination or going to the toilet more often than usual	☐	☐	☐	☐
5. Urgency of urination or an uncontrollable urge to pass urine	☐	☐	☐	☐

Mild: Symptom barely noticeable to the subject or does not make the subject uncomfortable; it does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of the symptom.

Moderate: Symptom of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of the symptom may be needed.

Severe: Symptom of a sufficient severity to cause the subject severe discomfort. Treatment for the symptom is needed.

STUDY W-5222-301 DAILY SYMPTOM ASSESSMENT QUESTIONNAIRE

[Page 1 of 2]

Instructions for the Daily Symptom Assessment questionnaire (to capture new/current cUTI/AP Symptoms) to be administered to the subject at the following visits: Screening, Day 1 to EOT, TOC, and LFU (*read aloud to the subject*):

"This questionnaire asks about your urinary tract infection symptoms in the past 24 hours.

Please respond whether you have had any of the following symptoms or problems in the past 24 hours and how severe they were. Answer each question by choosing only one response from the following possible options: No symptoms, mild symptoms, moderate symptoms, or severe symptoms."

STUDY W-5222-301 DAILY SYMPTOM ASSESSMENT QUESTIONNAIRE

[Page 2 of 2]

Site:	
Subject Number:	
Visit:	
Date (DD/MM/YYYY):	
Assessment Time (24-h Clock):	

Symptom Assessment	No Symptom	Mild	Moderate	Severe
1. Lower back or flank pain (Please show the figure indicating the flank area to the subject)	☐	☐	☐	☐
2. Pain or uncomfortable pressure in the lower abdomen or pelvic area	☐	☐	☐	☐
3. Pain or burning during urination	☐	☐	☐	☐
4. Frequent urination or going to the toilet more often than usual	☐	☐	☐	☐
5. Urgency of urination or an uncontrollable urge to pass urine	☐	☐	☐	☐

Mild: Symptom barely noticeable to the subject or does not make the subject uncomfortable; it does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of the symptom.

Moderate: Symptom of a sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of the symptom may be needed.

Severe: Symptom of a sufficient severity to cause the subject severe discomfort. Treatment for the symptom is needed.

APPENDIX IV PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Study Title:	A Phase 3, Randomized, Double-blind, Multicenter, Comparative Study to Determine the Efficacy and Safety of Cefepime-zidebactam vs. Meropenem in the Treatment of cUTI or AP in Adults
Protocol Number:	W-5222-301
IND Number:	116002
EudraCT Number:	2019-002768-28
Protocol Version:	Global Amendment 1, version 2.0
Date Amended:	14 DEC 2021
Sponsor:	Wockhardt Bio AG Grafenauweg 6 Zug-6300, Switzerland Phone: +41-417275220 Fax: +41-417275221

I have read and I understand Protocol W-5222-301, Global Amendment 1, version 2.0, dated 14 DEC 2021. I agree to the following:

- To conduct the clinical study in compliance with Good Clinical Practice (GCP), with applicable regulatory requirements and laws, with the protocol agreed to by the Sponsor and given approval/favorable opinion by my Independent Ethics Committee/ Institutional Review Board of record
- To comply with procedures for data handling, recording/reporting and maintenance of confidentiality
- To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives and partners, and any regulatory authorities
- To retain the essential documents in the study and institution files until the Sponsor informs me or the institution that these documents are no longer needed
- To provide copies of the protocol, any subsequent protocol amendments, and access to all information provided by the Sponsor to the study personnel under my supervision; I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol

_____

Investigator name (print)

_____ _____

Investigator signature Date

CYGNATURE

W-5222-301 Protocol Global AM1 ver 2.0 Final 14Dec21

Completed

Document information

Document ID :
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