STUDY NUMBER: VNRX-5133-201

PROTOCOL TITLE: A Phase 3, Randomized, Double-blind, Active-controlled Noninferiority Study Evaluating the Efficacy, Safety, and Tolerability of Cefepime/VNRX-5133 in Adults with Complicated Urinary Tract Infections, Including Acute Pyelonephritis

NCT Number: NCT03840148

Document Date: 10 December 2019

DRUG:	VNRX-5133
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IND NUMBER:	126702
EUDRACT NUMBER:	2018-001451-13
SPONSOR:	VenatoRx Pharmaceuticals, Inc. (VenatoRx) [redacted]
ORIGINAL GLOBAL PROTOCOL DATE:	30 October 2018
PROTOCOL AMENDMENT NUMBER:	2
VERSION NUMBER:	3.0
VERSION DATE:	10 December 2019

CLINICAL PROTOCOL APPROVAL FORM

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States state and federal regulations, all other applicable local regulatory requirements, and ICH guidelines. Any modification of the clinical study protocol must be documented in writing by the sponsor.

Sponsor: VenatoRx Pharmaceuticals, Inc. (VenatoRx)

Signed: [redacted] **Date:** 10-Dec-2019

SUMMARY OF CHANGES

Current Amendment 2	
Version No., Date:	3.0, 10-Dec-2019
Replaces Previous Version No, Date.	2.0, 30-Jan-2019

Change 1: Inclusion/Exclusion Criteria	
Description: Change of unit in Inclusion #4	
Section	**Revision**
Synopsis 4.0	WBC >10 cells per high power field in urine sediment WBC > 10 cells per high power field in urine sediment

Change 2: Study Endpoints	
Description: Clarification to the Primary Endpoint and updates to the Secondary Endpoints	
Section	**Revisions**
Synopsis/3.2/10.3.5	**Primary Endpoint:** Microbiological success is defined as any gram negative bacterial pathogen found at study entry are eradicated to $<10^3$ colony forming units per microliter **Secondary Endpoints:** Old version: The proportion of patients with both microbiological success and symptomatic clinical success at TOC in the extended microITT population The proportion of patients with per-patient microbiological success at TOC in the microbiologically evaluable (ME)-TOC population The proportion of patients with symptomatic clinical success at TOC in the clinically evaluable (CE)-TOC and ME-TOC populations The proportion of patients with clinical success based on investigator opinion at EOT, TOC, and

	LFU in the microITT and relevant CE and ME populations The proportion of patients with per-patient microbiological success at EOT and LFU in the microITT, ME-EOT, and ME-LFU populations The proportion of patients with symptomatic clinical success at EOT and LFU in the microITT, CE-EOT, ME-EOT, CE-LFU, and ME-LFU populations The proportion of patients with per-pathogen microbiological success in the microITT, ME-EOT, ME-TOC, and ME-LFU populations The proportion of patients with per-patient microbiological success among those with cefepime-resistant pathogens in the microITT, ME-EOT, ME-TOC, and ME-LFU populations The proportion of patients with per-pathogen microbiological success among those with cefepime-resistant pathogens in the microITT, ME-EOT, ME-TOC, and ME-LFU populations The proportion of patients with symptomatic clinical success among those with cefepime-resistant pathogens in the microITT, CE-EOT, CE-TOC, CE-LFU, ME-EOT, ME-TOC, and ME-LFU populations New version:

	The proportion of patients with both microbiological success and symptomatic clinical success at TOC in the extended microITT population, clinically evaluable (CE)-TOC and microbiologically evaluable (ME)- TOC populations The proportion of patients with both microbiological success and symptomatic clinical success at EOT in the micro-ITT, ME-EOT and CE-EOT populations, and at LFU in the micro-ITT, ME-LFU and CE-LFU populations The proportion of patients with per-patient microbiological success at EOT, TOC and LFU in the micro-ITT population andME- EOT, ME-TOC and ME-LFU populations The proportion of patients with symptomatic clinical success at EOT, TOC and LFU in the micro-ITT population andCE-EOT, CE-TOC and CE-LFU populations The proportion of patients with clinical success based on investigator opinion at TOC in the micro-ITT population The proportion of patients with per-pathogen microbiological success at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations The proportion of patients with both microbiological success and symptomatic clinical success among those with cefepime-resistant pathogens at EOT in the micro-ITT, ME-EOT and CE-EOT populations, TOC in the micro-ITT, ME-TOC, and CE-TOC populations, and at LFU in the micro-ITT, ME-LFU and CE-LFU populations The proportion of patients with per-patient microbiological success among those with cefepime-resistant pathogens at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations The proportion of patients with per-pathogen microbiological success among those with

	cefepime-resistant pathogens at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations The proportion of patients with symptomatic clinical success among those with cefepime-resistant pathogens at EOT in the micro-ITT and CE-EOT populations, TOC in the micro-ITT and CE-TOC populations, and at LFU in the micro-ITT and CE-LFU populations

Change 3: Statistical Analysis	
Description: Clarification to ME-EOT, ME-TOC and ME-LFU populations	
Section	**Revision**
Synopsis/10.3.1	Both study drugs are known to have antibacterial activity against all baseline gram negative pathogens Were evaluated at the respective EOT, TOC and LFU visits with a microbiological response of eradication or persistence (ie, per-patient microbiologic response of success or failure)

Change 4: Study Drug Management	
Description: Clarification to the treatment duration for patients without bacteremia	
Section	**Revision**
5.4	All patients will receive 7 days of IV treatment. Based on the scheduled study drug administration for patients without bacteremia, the patients could complete treatment of study day 7 or study day 8. All non-bacteremic patients (who do not require dosing adjustments for renal dysfunction) will receive at least 19 doses and no more than 21 doses of study drug. Added patients are not permitted to continue oral antibiotics at home prophylactically. Added the Investigator should continually assess whether the study drug has failed (ie, the patient has signs and symptoms of cUTI that have not improved or have recurred such that additional antibiotic therapy is warranted) and rescue therapy is required.

Change 5: Study Conduct	
Description: Added criteria as a result of feedback from SUKL (Czech Republic)	
Section	**Revision**
6.3.1	Added AST or ALT ≥10X ULN

Change 6: Description of Study Procedures	
Description: Added language to the Definition of Success with treatment for asymptomatic bacteremia	
Section	**Revision**
Table 8	Added treatment of asymptomatic bacteremia is prescribed based on the opinion of the investigator[2] [2] According to guidelines in both Europe and the United States, treatment of asymptomatic bacteriuria (the presence of 1 or more species of bacteria growing in the urine irrespective of the presence of pyuria, in the absence of signs or symptoms attributable to UTI) is in most cases not beneficial and may be harmful. Based on standard of care and protocol restrictions surrounding use of additional antibiotics, patients in this trial should not receive additional antibiotic for asymptomatic bacteriuria. Additional therapy should only be given if signs and symptoms warrant ongoing treatment for symptomatic cUTI (i.e., based on their clinical course in the absence of microbiological data).

Change 7: Description of Study Procedures	
Description: Added note to ethnicity	
Section	**Revision**
7.8.2	Added Ethnicity variable should only be used for African Americans

Change 8: Adverse Event Assessment and Reporting	
Description: Clarified criteria as a result of feedback from SUKL (Czech Republic)	
Section	**Revision**
8.6.1	Added laboratory abnormalities should be reported as adverse events if the result is considered to be clinically significant by the investigator.

Change 9: Other Reportable Events	
Description: Clarified pregnancy reporting	
Section	**Revision**
9.3	Added all pregnancies of female clinical study patients or partners of male study patients should be reported to sponsor. Added if written consent is obtained, monitoring should occur.

Change 10: Administrative
Description: Removed CRO from Signature Page and Replaced Sponsor Medical Representative

Previous Amendment 1	
Version No., Date:	2.0, 30-Jan-2019
Replaces Previous Version No, Date.	1.0, 30-Oct-2018

Change 1: Schedule of Events	
Description: Clarification regarding the assessments and procedures required at EOT when EOT occurs on Study Day 1.	
Section	**Revision**
Synopsis	Added patient is alive, and patient has not received additional antibacterial therapy for cUTI.
7.3	Added or in the event that EOT occurs on Study Day 1.
Table 1	Added EOT occurs on Study Day 1 or to Footnote 4.

Change 2: Study Endpoints	
Rationale: Updates to the definitions used for the study endpoints in response to regulatory feedback from the European Medicines Agency, including a definition of symptomatic clinical failure that includes use of additional antibiotics for the treatment of cUTI occurring after end of treatment.	
Section	**Revision**
Synopsis	Added patient is alive, and patient has not received additional antibacterial therapy for cUTI
3.2	Added patient is alive, and patient has not received additional antibacterial therapy for cUTI.
7.7.1	Modified Table 4 to specify at EOT and removed LFU and TOC: Added patient is alive to definition of symptomatic clinical response. Added Table 5: Symptomatic Response Criteria at TOC and LFU

Change 3: Time Windows for Pharmacokinetic Assessments	
Rationale: Correction of an error in the collection window at Study Day 3.	
Section	**Revision**
7.1	Table 10: Study Day 3 collection window deleted 7 hours and added 5 hours. Deleted all times shown are relative to the start of the infusion from the footnote.

VNRX-5133-201

A Phase 3, Randomized, Double-blind, Active-controlled Noninferiority Study Evaluating the Efficacy, Safety, and Tolerability of Cefepime/VNRX-5133 in Adults with Complicated Urinary Tract Infections, Including Acute Pyelonephritis

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to VNRX-5133 are the confidential and proprietary information of VenatoRx Pharmaceuticals, Inc. (VenatoRx), and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of VenatoRx.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Council on Harmonisation guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study site personnel under my supervision copies of the protocol and any amendments, and access to all information provided by VenatoRx or specified designees. I will discuss the material with them to ensure that they are fully informed about VNRX-5133 and the study.

Investigator Name (printed)	Signature
Date	Site Number

**The protocol should be signed by the local investigator who is responsible for the study implementation at his/her specific site; i.e., if Investigational New Drug study, the individual who signs the Form FDA 1572.*

STUDY SUMMARY

Title:	A Phase 3, Randomized, Double-blind, Active-controlled Noninferiority Study Evaluating the Efficacy, Safety, and Tolerability of Cefepime/VNRX-5133 in Adults with Complicated Urinary Tract Infections, Including Acute Pyelonephritis
Phase of Study:	Phase 3
Target Population:	Adult male and female patients with complicated urinary tract infection (cUTI), including acute pyelonephritis (AP)
Number of Patients:	582 patients will be randomized into 2 groups in a 2:1 ratio (388 patients to cefepime/VNRX-5133; 194 patients to meropenem)
Number of Sites:	Approximately 122 sites in the United States and other countries
Study Duration:	Approximately 14 months
Duration of Treatment:	7 days (up to 14 days for patients with bacteremia)
Drug Administered:	**Test:** Cefepime/VNRX-5133 (2 g/0.5 g intravenously [IV] every 8 hours [q8h]) **Active comparator:** Meropenem (1 g IV q8h)
Study Drug Administration:	All study drugs will be provided by the sponsor. For cefepime/VNRX-5133, cefepime hydrochloride (2 g/vial, sterile, white to pale yellow powder) and VNRX-5133 (0.5 g/vial sterile, white to yellow powder) will each be reconstituted independently, then combined into a single IV bag, and diluted with 0.9% sodium chloride solution for IV injection. Cefepime/VNRX-5133 will be administered q8h via IV pump over a 2-hour period. In order to maintain the blind, patients randomized to cefepime/VNRX-5133 will also receive meropenem placebo (0.9% sodium chloride solution) administered via IV pump over 30 minutes. Meropenem (1 g/vial) will be reconstituted in a single IV bag and will serve as active comparator for IV injection. Meropenem will be administered q8h via IV pump over 30 minutes. In order to maintain the blind, patients randomized to meropenem will also receive cefepime/VNRX-5133 placebo (0.9% sodium chloride solution) administered via IV pump over a 2-hour period. Study drug and placebo IV bags as well as IV tubing will be blinded with sleeves. All patients will be treated for 7 days of IV therapy. Patients with bacteremia may receive up to 14 days of treatment at the investigator's discretion.

All study drugs will be prepared at the study site by an unblinded pharmacist or designee. A separate unblinded study monitor will periodically review pharmacy logs and drug accountability. The sponsor clinical team, investigator, patients, and all other study staff will remain blinded to study drug.

Objectives:

Primary objective:

- To assess the efficacy of cefepime/VNRX-5133 compared with meropenem with respect to both per-patient microbiologic eradication and symptomatic resolution of all urinary tract infection (UTI)-core symptoms (or return to pre-morbid baseline) at the Test of Cure (TOC) visit

Secondary objectives:

- To determine the efficacy of cefepime/VNRX-5133 compared with meropenem with respect to the per-patient microbiological response, per-pathogen microbiologic response, and symptomatic resolution of all UTI-core symptoms at various timepoints in various populations
- To determine the efficacy of cefepime/VNRX-5133 compared with meropenem with respect to the per-patient microbiological response, per-pathogen microbiologic response, and symptomatic resolution of all UTI-core symptoms in patients with cUTI due to cefepime-resistant pathogens at various timepoints in various populations
- To evaluate the safety and tolerability profile of cefepime/VNRX-5133 compared with meropenem in the treatment of patients with a cUTI in the safety population
- To evaluate the steady-state pharmacokinetics (PK) of cefepime and VNRX-5133 in patients using a population PK model

Study Design:

Study VNRX-5133-201 is a Phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled noninferiority study to evaluate the efficacy, safety, and tolerability of cefepime/VNRX-5133 compared with an active control, meropenem, in adult patients with cUTI, including AP. Each patient is expected to complete the study within approximately 4 to 5 weeks.

After obtaining signed informed consent and confirming eligibility within 24 hours prior to randomization, patients will be randomized in a 2:1 ratio to receive either cefepime/VNRX-5133

(2 g/0.5 g IV q8h) or the active comparator, meropenem (1 g IV q8h) on Study Day 1.

Patients will be stratified by the type of infection (AP only versus complicated lower UTI with or without AP) and by region (North America and Western Europe versus Eastern Europe versus rest of the world). At least 30% of the population will have AP.

Patients may receive up to 24 hours of antibacterials for treatment of cUTI prior to randomization; however, the number of patients with prior antibacterial use will be limited to approximately 25% of the population. Before receipt of study drug, a urine specimen and blood cultures will be obtained from all patients for culture and for *in vitro* antibacterial susceptibility testing. Patients with an indwelling catheter should have urine samples collected following the placement of a new catheter, or if the indwelling catheter cannot be removed, aseptic techniques should be used through a properly disinfected collection port. Patients with an indwelling catheter should be randomized only if they are expected to permanently discontinue use of the catheter prior to Study Day 5.

Screening assessments will also include a Daily Patient Symptom Questionnaire (DPSQ) and a Pre-morbid Patient Symptom Questionnaire (PPSQ). The DPSQ will be administered at screening, daily while on study drug, and at End of Treatment (EOT), TOC, and Late Follow-up (LFU) visits to determine the presence and intensity of cUTI symptoms. The PPSQ will be administered once at screening to determine whether a patient normally experiences urinary tract symptoms (i.e., in the absence of a UTI) that may be attributable to other disease processes (e.g., benign prostatic hyperplasia [BPH]).

Study drug will be administered IV for 7 days and will be considered completed after the third dose on Study Day 7 for patients without bacteremia. All patients (who do not require dosing adjustments for renal dysfunction) will receive at least 19 doses. Patients without bacteremia will receive a maximum of 21 doses of active study drug. Patients with bacteremia at study entry may have their treatment extended up to 14 days at the investigator's discretion.

Patients will be admitted at screening and remain at the study site or hospital for the duration of the IV treatment period and through the EOT visit. The EOT visit will be performed within 24 hours after the last dose of IV study drug. Patients may be discharged from the study site after the EOT visit if clinically stable and at the investigator's discretion.

Patients must return to the study site for the TOC visit (Study Days 19 to 23) and the LFU visit (Study Days 28 to 35).

Inclusion/Exclusion Criteria:

Patients must meet the following general inclusion criteria to be eligible for inclusion in the study:

1. Provide signed informed consent
2. Adult male or female, ≥18 years of age
3. If female, meets at least 1 of the following criteria:

- Surgically sterile
- Age ≥50 years and postmenopausal for ≥12 months
- Age <50 years and postmenopausal for ≥2 years
- Patient has a negative serum pregnancy test and agrees not to attempt pregnancy and, if participating in sexual activity, agrees to use an effective dual method of contraception

4. Patient has pyuria as demonstrated by at least 1 of the following:

- Urine dipstick positive for leukocyte esterase
- White blood cells (WBC) >10 cells/µL in unspun urine
- WBC >10 cells per high power field (HPF) in urine sediment

5. Demonstrates either AP or complicated lower UTI as defined by the following criteria:

a. AP is indicated by the presence of both of the following criteria:

- At least 1 of the following is present:
  - Nausea or vomiting
  - Chills or rigors or warmth associated with fever, defined as body temperature >38°C
- Has flank pain or costovertebral angle tenderness

b. Complicated lower UTI is indicated by the presence of all 3 of the following criteria:

- At least 1 of the following is present:
    - Nausea or vomiting
    - Chills or rigors or warmth associated with fever, defined as body temperature >38°C
- At least 1 of the following signs/symptoms is present:
    - Dysuria
    - Urinary urgency
    - Urinary frequency
    - Pelvic pain or suprapubic tenderness/pelvic tenderness
- At least 1 of the following complicating factors is present:
    - Chronic urinary retention
    - Obstructive uropathy (if complete obstruction, should intend to relieve obstruction within 48 hours after randomization)
    - Neurogenic bladder with presence or history of urine residual volume of >100 mL
    - Indwelling catheter (with expectation for permanent discontinuation of the catheter by Study Day 5)

6. Requires IV antibacterial therapy as initial treatment for cUTI

Patients who meet any of the following general exclusion criteria will not be eligible for inclusion in the study:

1. Receipt of effective antibacterial drug therapy for cUTI for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization
2. Where a urine culture result is available:

- At least 1 uropathogen at $\geq 10^5$ colony forming units per milliliter (CFU/mL) is resistant to meropenem, or
- A gram-negative bacterial pathogen is not identified
- More than 2 microorganisms are isolated regardless of the colony count, or

- The patient has a confirmed fungal UTI with colony count $\geq 10^3$ CFU/mL

3. Requirement for use of nonstudy systemic antibacterial drug therapy that would have a potential effect on outcome evaluations in patients with cUTI

4. Patients with suspected or confirmed prostatitis or urinary tract symptoms attributable to a sexually transmitted disease

5. Patients with perinephric or renal abscess

6. Patients with renal transplantation or receiving hemodialysis or peritoneal dialysis

7. Patients with urinary diversions (e.g., ileal loops, cutaneous urostomy)

8. Patients who may need ongoing antibacterial drug prophylaxis after treatment of cUTI (such as vesico-ureteral reflux)

9. Any recent history of trauma to the pelvis or urinary tract

10. Patient has any urinary catheter or device or foreign body that will not be discontinued by Study Day 5, including but not limited to indwelling bladder catheter, urinary catheter, nephrostomy tubes, or stent

11. Patient is unlikely to respond to 7 days of antibacterial therapy for the treatment of cUTI without bacteremia or up to 14 days of therapy for treatment of cUTI with bacteremia

12. Patient has acute hepatitis, cirrhosis (Child-Pugh Class B or C), acute hepatic failure, or acute decompensation of chronic hepatic failure

13. Patient has had a heart, lung, heart-lung, or pancreatic transplant at any time; or bone marrow transplant in the preceding year

14. Patient has any of the following laboratory values:

- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 calculated by the Modification of Diet in Renal Disease (MDRD) formula[2]

- Hematocrit <25% or hemoglobin <8 g/dL

- Platelet count <50,000/mm^3

- Total bilirubin >3.0× the upper limit of normal (ULN), unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert's disease

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0× ULN at screening. Patients with values >3.0× ULN and <5.0× ULN are eligible if these values are acute and documented as being directly related to the infectious process being treated.

- Alkaline phosphatase >3.0× ULN. Patients with values >3.0× ULN and <5.0× ULN are eligible if this value is acute and documented as being directly related to the infectious process being treated.

15. Patient has a history of serious hypersensitivity (e.g., anaphylaxis), serious allergy, or any serious reaction to cephalosporin, penicillin, carbapenem, or other β-lactam antibacterials

16. Patient is considered unlikely to survive the 4- to 5-week study period or have a rapidly progressive or terminal illness, including septic shock, that is associated with a high risk of mortality

17. Patient requires concomitant medication with valproic acid or divalproex

18. Patient is in a situation or has a condition that, in the investigator's opinion, may interfere with optimal participation in the study, or is unlikely to comply with protocol (e.g., inability to fully comprehend and clearly respond to questions on the PPSQ and DPSQ in a reliable manner, uncooperative attitude, inability to return for follow-up visit, or unlikely to complete the study)

19. Patient is participating in any other clinical study that involves the administration of an investigational product at

the time of presentation or during the course of the study or has received treatment with an investigational product in the 30 days prior to study enrollment

20. Female patients who are pregnant, lactating, or planning to become pregnant during this study

Primary Endpoint: The primary endpoint is the demonstration of microbiological success (any gram negative bacterial pathogens found at study entry are eradicated to $<10^3$ CFU/mL on urine culture) and the demonstration of symptomatic clinical success (symptomatic resolution or return to pre-morbid baseline of all UTI-core symptoms including frequency, urgency, dysuria, suprapubic/pelvic pain, and flank pain, patient is alive, and patient has not received additional antibacterial therapy for cUTI) at TOC in the microbiological intent-to-treat (microITT) population.

Secondary Endpoints: **Clinical and Microbiological Efficacy:**

- The proportion of patients with both microbiological success and symptomatic clinical success at TOC in the extended microITT population, clinically evaluable (CE)-TOC and microbiologically evaluable (ME)- TOC populations
- The proportion of patients with both microbiological success and symptomatic clinical success at EOT in the micro-ITT, ME-EOT and CE-EOT populations, and at LFU in the micro-ITT, ME-LFU and CE-LFU populations
- The proportion of patients with per-patient microbiological success at EOT, TOC and LFU in the micro-ITT, ME- EOT, ME-TOC and ME-LFU populations
- The proportion of patients with symptomatic clinical success at EOT, TOC and LFU in the micro-ITT population and CE-EOT, CE-TOC and CE-LFU populations
- The proportion of patients with clinical success based on investigator opinion at TOC in the micro-ITT population
- The proportion of patients with per-pathogen microbiological success at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations

- The proportion of patients with both microbiological success and symptomatic clinical success among those with cefepime-resistant pathogens at EOT in the micro-ITT, ME-EOT and CE-EOT populations, TOC in the micro-ITT, ME-TOC, and CE-TOC populations, and at LFU in the micro-ITT, ME-LFU and CE-LFU populations

- The proportion of patients with per-patient microbiological success among those with cefepime-resistant pathogens at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations

- The proportion of patients with per-pathogen microbiological success among those with cefepime-resistant pathogens at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations

- The proportion of patients with symptomatic clinical success among those with cefepime-resistant pathogens at EOT in the micro-ITT and CE-EOT populations, TOC in the micro-ITT and CE-TOC populations, and at LFU in the micro-ITT and CE-LFU populations

Safety and Tolerability:

- Safety and tolerability will be assessed based on the incidence and severity of adverse events (AEs) and serious adverse events (SAEs), exposure, mortality, reasons for discontinuation of study drug and study withdrawal, vital sign measurements, and clinically significant changes in clinical chemistry, hematology, urinalysis, and coagulation laboratory values.

Pharmacokinetics:

- The population PK analysis using data from the study will be described in a population PK analysis plan and summarized in a separate report.

Resolution of Fever:

- The time to first defervescence (≤37.8°C) in the microITT population for patients who have fever (>38°C) at baseline will be assessed as an exploratory endpoint.

Statistical Analysis: The study will randomize 582 patients with cUTI into 2 groups in a 2:1 ratio (388 patients to cefepime/VNRX-5133; 194 patients to meropenem). The sample size was selected based on an anticipated evaluability rate of 68%, a response rate of 75%, 90% power, a 2-sided alpha of 0.05, and a noninferiority margin of 15%.

Study endpoints will be analyzed in the following populations:

- Intent-to-treat (ITT) population: all randomized patients
- microITT population: all patients randomized to treatment AND
    - Had a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a gram-negative pathogen against which both cefepime/VNRX-5133 and meropenem have antibacterial activity AND
    - Had no more than 2 microorganisms identified in the study entry culture regardless of colony count
- Extended microITT population: all patients randomized to treatment AND
    - Had a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a gram-negative pathogen against which at least 1 study drug (i.e., cefepime/VNRX-5133 and/or meropenem) have antibacterial activity AND
    - Had no more than 2 microorganisms identified in the study entry culture regardless of colony count
- CE-EOT, CE-TOC, and CE-LFU populations: all patients who meet the definition for the ITT population AND
    - Had an appropriate diagnosis of cUTI
    - Received treatment for ≥48 hours (or <48 hours if discontinued due to an AE or death)

- Were evaluated for the appropriate endpoint at the relevant timepoint (i.e., EOT, TOC, and LFU) with an outcome that is not indeterminate
- Did not violate entry criterion surrounding use of prior antibacterials
- Did not receive a concomitant systemic antibiotic with potential activity against any of the baseline pathogens between the time of randomization and EOT, TOC, and LFU, respectively, except therapies used to treat cUTI in patients who have failed study drug
- Did not have other confounding factors that interfered with the assessment of outcome as assessed by a blinded evaluability team prior to database lock

- ME-EOT, ME-TOC, and ME-LFU populations: all patients who meet the criteria for the microITT population AND
  - Both study drugs are known to have antibacterial activity against the baseline gram-negative pathogens and had an appropriate diagnosis of cUTI
  - Received treatment for ≥48 hours (or <48 hours if discontinued due to an AE or death)
  - Were evaluated at the respective EOT, TOC, and LFU visits with a microbiological response of eradication or persistence (i.e., per-patient microbiologic response of success or failure)
  - Did not violate entry criterion surrounding use of prior antibacterials
  - Did not receive a concomitant systemic antibiotic with the potential activity against any of the baseline pathogens between the time of randomization and EOT, TOC, and LFU, respectively, except therapies used to treat cUTI in patients who have failed study drug

- Did not have other confounding factors that interfered with the assessment of outcome as assessed by a blinded evaluability team prior to database lock

- Safety population: all patients who receive any dose of study drug

Continuous clinical variables will be summarized descriptively (i.e., patient count, mean, standard deviation, median, minimum, and maximum). Categorical data will be summarized descriptively with frequencies and percentages based on the number of patients exposed within a treatment.

Full details of the statistical analysis will be described in the statistical analysis plan.

The population PK analysis methods using data from the study will be described in a population PK analysis plan, and the population PK modeling will be summarized in a separate report.

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Procedure and Assessment	Screening[1]	Treatment Period		EOT[4] (Within 24 hours of last IV dose)	TOC[5] (Study Days 19-23)	LFU[6] (Study Days 28-35)	Section of Protocol
		Day 1[2]	Study Days 2-7 (up to Study Day 14 for patients with bacteremia)[3]				
Informed consent	X						4.4
Confirm eligibility	X						4.2, 4.3
Medical history	X						7.9.1
Demographics	X						7.9.1
Randomization[7]		X					6.1
Prior and concomitant medications (including antibiotics)	X	X	Daily	X	X	X	7.9.2
Complete physical examination	X						7.9.3
UTI-focused physical examination[8]	X	X[9]	Daily	X	X	X	7.9.3
DPSQ	X	X[9]	Daily	X	X	X	7.7.1
PPSQ	X						7.7.1
Height and weight	X						7.9.4
Vital signs[10]	X	X[9]	Daily	X	X	X	7.8.1
eGFR[11]	X		Repeat using local serum creatinine measurements as clinically indicated				7.8.2
12-lead ECG[12]	X		On Study Day 4 and as clinically indicated				7.8.3
Urine for dipstick or microscopy[13]	X						7.8.4
Quantitative urine culture	X			X	X	X	7.7.4.1

Procedure and Assessment	Screening[1]	Treatment Period		EOT[4] (Within 24 hours of last IV dose)	TOC[5] (Study Days 19-23)	LFU[6] (Study Days 28-35)	Section of Protocol
		Day 1[2]	Study Days 2-7 (up to Study Day 14 for patients with bacteremia)[3]				
Blood cultures	X		For patients with positive baseline blood cultures, repeat every 2 to 3 days until negative. Also perform as clinically indicated.				7.7.4.2
Serum and urine β-HCG[14]	X						7.8.4
Blood and urine for clinical laboratory safety assessments[15]	X		Study Day 4; Study Days 8 and 12 if still on study drug	X	X	X	7.8.4
Plasma sampling for PK[16]		X	Study Days 2 and 3 only				7.10
AE monitoring	X	X	Daily	X	X	X	7.8.5
Study drug administration		X	Daily				5.3
Investigator Opinion of Clinical Response				X	X	X	7.7.5

β-hCG=beta-human chorionic gonadotropin; AE=adverse event; DPSQ=Daily Patient Symptom Questionnaire; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOT=End of Treatment; IV=intravenous; LFU=Late Follow-up; MDRD=Modification of Diet in Renal Disease; PK=pharmacokinetics; PPSQ=Pre-morbid Patient Symptom Questionnaire; q8h=every 8 hours; TOC=Test of Cure; UTI=urinary tract infection; WBC=white blood cell.

1 Perform screening assessment prior to first dose of IV study drug. Assessments performed as part of routine standard of care prior to consent (e.g., blood culture, laboratory tests) may be used to satisfy screening requirements; however, no study-specific procedures may be performed prior to informed consent.

2 Administration of the first dose of IV study drug marks the beginning of Study Day 1. Subsequent study days are based on calendar days.

3 The duration of treatment with study drug will be 7 days. Patients with bacteremia at study entry may have their treatment extended up to 14 days at the investigator's discretion.

4 EOT visit will be performed within 24 hours after the last dose of IV therapy. When EOT occurs on the same calendar day as the last day of IV therapy, any assessments already performed on that calendar day do not need to be repeated, unless EOT occurs on Study Day 1 or clinically indicated based on the investigator's judgement.

5 TOC visit will occur between Study Days 19 and 23.

6 LFU visit will occur between Study Days 28 and 35.

7 Randomization will occur after screening and prior to first dose of study drug. It may be on the same calendar day as Study Day 1 or on the previous calendar day.

8 A UTI-focused physical examination includes assessment of costovertebral angle tenderness and suprapubic/pelvic tenderness.

9 UTI-focused physical examination, DPSQ, and vital signs do not need to be repeated on Study Day 1 if screening and Study Day 1 occur on the same calendar day.
10 Record vital signs (heart rate, respiratory rate, temperature [oral or tympanic], and blood pressure). If more than 1 set of vital signs is acquired on a given calendar day, the highest temperature and the heart rate, respiratory rate, and blood pressure associated with that temperature (or those acquired nearest to that temperature) will be recorded.
11 Calculate eGFR using the MDRD formula at screening. If the investigator (or designee) determines that calculation of eGFR during the treatment period is warranted postbaseline (e.g., due to change in clinical status or for evaluation of need for dose change), local laboratory serum creatinine should be used and the results should be reported as an unscheduled laboratory test. See Section 7.8.2 for details for the calculation of eGFR.
12 ECGs will be performed at screening and on Study Day 4 immediately after completion of cefepime/VNRX-5133 or cefepime/VNRX-5133 placebo infusion.
13 To demonstrate pyuria during screening, microscopy evaluation of urine for the identification of at least 10 WBCs per cubic millimeter OR microscopic evaluation of at least 10 WBCs per high-power field in urine sediment may be performed OR a urinary dipstick for the presence of leukocyte esterase may be performed during screening.
14 Serum β-hCG must be performed as part of screening/eligibility in women of childbearing potential. A patient may begin study drug on the basis of a negative urine β-hCG performed at a local laboratory, but a serum β-hCG test must still be sent to the central laboratory for confirmation.
15 Blood and urine specimens at screening will be sent to a local laboratory to confirm eligibility for randomization. Specimens will be also sent to the central laboratory at the timepoints noted in the table.
16 Sparse PK sampling timepoints are detailed in Section 7.10.

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β-hCG	beta-human chorionic gonadotropin
AE	adverse event
ALT	alanine aminotransferase
AP	acute pyelonephritis
AST	aspartate aminotransferase
BPH	benign prostatic hyperplasia
BUN	blood urea nitrogen
CE	clinically evaluable
CFU	colony forming unit
CI	confidence interval
cIAI	complicated intra-abdominal infection
CK	creatine kinase
CRE	carbapenem-resistant *Enterobacteriaceae*
CRO	contract research organization
CSR	clinical study report
cUTI	complicated urinary tract infection
DPSQ	Daily Patient Symptom Questionnaire
DSMB	data and safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	End of Treatment
ESBL	extended-spectrum β-lactamase
GCP	Good Clinical Practice
HPF	High Power Field
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LFU	Late Follow-up
MDR	multidrug resistance
MDRD	Modification of Diet in Renal Disease
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimal inhibitory concentration
microITT	microbiological intent-to-treat
PD	pharmacodynamic
PK	pharmacokinetic(s)
PPSQ	Pre-morbid Patient Symptom Questionnaire
PT	preferred term
PTT	partial thromboplastin time
q8h	every 8 hours
q12h	every 12 hours
RBC	red blood cell
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure

TEAE	treatment-emergent adverse event
TOC	Test of Cure
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
UTI	urinary tract infection
VNRX	VenatoRx Pharmaceuticals, Inc. (VenatoRx)
WBC	white blood cell
WMA	World Medical Association

1 INTRODUCTION AND RATIONALE

1.1 Background

The β-lactam class of antibiotics, because of their efficacy and safety profile, are the most widely used class of antibacterial drugs in both the community and hospital settings. However, the utility of all members of this class of drugs is being threatened by the spread of new β-lactamases in gram-negative pathogens with a very broad spectrum of hydrolyzing activity. While different β-lactam class drugs (i.e., penicillins, cephalosporins, monobactams, and carbapenems) are differentially affected by various enzymes, no members of the class are unscathed.[1]

VNRX-5133 is a non-β-lactam β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-β-lactamases (i.e., Ambler Classes A, B, C, and D). VNRX-5133, in combination with cefepime, has the potential to address the serious unmet medical need for a safe and effective therapy for treatment of infections caused by multidrug resistant (MDR) gram-negative bacteria, particularly extended-spectrum β-lactamase-producing organisms and carbapenem-resistant *Enterobacteriaceae* (CRE) and *Pseudomonas aeruginosa*.

Cefepime is a broad-spectrum, fourth-generation cephalosporin antibiotic administered intravenously (IV) that has been in clinical use for over 2 decades for the treatment of serious infections, including moderate to severe pneumonia, complicated urinary tract infections (cUTIs), and complicated intra-abdominal infections (cIAIs).

VenatoRx Pharmaceuticals, Inc. (VenatoRx) is developing VNRX-5133 for use in combination with cefepime for the treatment of cUTI, a disease that has been associated with an alarming increase in the incidence of MDR β-lactamase-producing organisms.

cUTI is defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen on a culture of urine or blood accompanied by local and systemic signs and symptoms, including fever, chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness, that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Patients with acute pyelonephritis (AP), regardless of underlying abnormalities of the urinary tract, are considered a subset of patients with cUTIs.

VNRX-5133 in combination with cefepime has demonstrated potent *in vitro* activity against CRE and *P aeruginosa* based on 90% minimal inhibitory concentration (MIC) determinations. Several *in vitro* studies have also shown that the antibacterial activity of cefepime/VNRX-5133 is largely unaffected by the presence of urine, with most MICs determined in the presence of urine within one doubling dilution of MICs determined in its absence (LSI study VNRX-001-16; IHMA study 2931). A comprehensive nonclinical safety assessment program was conducted to support further clinical studies with VNRX-5133. The initial safety, tolerability, and pharmacokinetics (PK) study of cefepime/VNRX-5133 when administered IV to human subjects has been previously evaluated in Phase 1 studies. Cefepime/VNRX-5133 was well tolerated in these studies.

A detailed summary of the available nonclinical and clinical data for cefepime/VNRX-5133 is provided in the Investigator's Brochure (IB).[1]

1.2 Study Rationale

Cefepime/VNRX-5133 is being developed as an IV antibiotic formulation in combination for the treatment of patients with serious gram-negative bacterial infections. The strategy of using β-lactam/β-lactamase inhibitor combinations for treatment of infections caused by β-lactamases-producing pathogens has been successful in a variety of bacterial infections. Gram-negative pathogens, including those producing extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, and carbapenemases, are important causes of cUTIs. The spectrum of activity of cefepime/VNRX-5133 is well suited for the treatment of pathogens commonly responsible for cUTIs.

Meropenem has been selected as the comparator because it has demonstrated efficacy against gram-negative pathogens isolated in cUTIs, including pyelonephritis. Although meropenem is approved for other indications, including cIAI, skin and soft tissue structure infections, and bacterial meningitis in pediatric patients, it is not approved for use in cUTI in the United States (US). However, meropenem is approved for cUTI in other geographic regions. Furthermore, carbapenems are the drugs of choice against ESBL-producing gram-negative pathogens, especially in serious infections. As such, it is an appropriate comparator to use when evaluating a new drug designed to treat infections due to bacteria harboring serine β-lactamases.

1.2.1 Dose Selection Rationale

For the cefepime/VNRX-5133 treatment group, the selected dose and infusion duration of cefepime/VNRX-5133 selected are expected to provide drug exposure that will result in a high probability of the PK/pharmacodynamic (PD) target attainment. A number of *in vitro* and *in vivo* PK/PD studies have been conducted to characterize the pharmacological basis of VNRX-5133 efficacy when combined with cefepime. The goals of these studies have been to 1) identify the PK/PD index that best describes the exposure-response relationship of VNRX-5133 administered in combination with cefepime and 2) characterize the magnitude of the PK/PD index required for various degrees of bacterial killing. In addition, the results from the nonclinical PK/PD studies conducted to date, the human PK data collected in Phase 1 studies, and human plasma protein binding data were used to select human therapeutic doses. Lastly, the probability of PK/PD target attainment in clinical efficacy studies was further explored by the construction of a population PK model based on Phase 1 data and use of Monte Carlo simulations. Taken together, these data demonstrate that a 0.5 g dose of VNRX-5133, when administered with cefepime 2 g every 8 hours (q8h), is expected to be highly effective, even after taking into account increased PK variability expected in a patient population compared to that observed in healthy volunteers in Phase 1 studies.

Cefepime/VNRX-5133 will be administered as an IV infusion over 2 hours.

Meropenem 1 g q8h will be given as an active comparator. In the US and elsewhere, meropenem is approved at doses of 0.5 or 1 g q8h, depending on the type of infection. The Summary of Product Characteristics indicates that doses of 0.5 or 1 g meropenem q8h is appropriate for cUTI.

In order to ensure the best therapy against pathogens that are more difficult to treat, the dose of 1 g has been chosen. Although meropenem is not approved in the US for cUTI, the US prescribing information indicates that 1 g meropenem q8h is appropriate for the treatment of patients with cIAIs and skin and soft tissue structure infections due to *P aeruginosa*, which is consistent with the goal to use a higher dose (i.e., 1 g) in more difficult-to-treat infections.

Patients with bacteremia at study entry may have their treatment extended up to 14 days at the investigator's discretion.

Additional details on human PK and clinical dosing regimen are provided in the IB.[1]

1.2.2 Patient Selection Rationale

The population enrolled into the study will include adult male and female patients with cUTI (AP or complicated lower urinary tract infection [UTI]). At least 30% of patients will be diagnosed with AP. Before receipt of study drug, urine specimen and blood cultures will be obtained from all patients for culture and for *in vitro* antimicrobial susceptibility testing. Patients known to have a pathogen with documented resistance to meropenem should be excluded from the study.

1.3 Benefit-Risk Assessment

The population for this study will comprise patients with cUTI that are of sufficient severity to require hospitalization and treatment with IV antibiotics. The potential benefit to participating patients is in receiving effective antibiotic treatment for their infections. The potential benefit of the study, in general, is the identification of a novel antibiotic combination product that is an effective treatment for cUTI in the face of the changing pattern of antibiotic resistance and the need for antibiotics to treat increasingly resistant bacteria. It is possible that cefepime/VNRX-5133 will not prove to be a sufficiently effective treatment for cUTIs (i.e., not as effective as the comparator treatment). This risk is mitigated in that the patients will be closely monitored and managed with appropriate therapies as determined by the investigator who is providing treatment.

The risk considerations for this study should encompass the known and potential risks for the development product cefepime/VNRX-5133 and its component products cefepime and VNRX-5133, as well as the marketed product meropenem. The risks for cefepime and meropenem are widely available in their respective prescribing information; such risks will not be discussed in this section.

The risks for cefepime/VNRX-5133 have not been fully elucidated; however, it is assumed that known or potential risks for cefepime/VNRX-5133 should include those identified in the clinical study experience with cefepime/VNRX-5133, VNRX-5133 alone, and cefepime alone. Potential risks for cefepime/VNRX-5133 include the occurrence of events seen with cefepime alone but may occur at a greater frequency and/or severity than those seen with cefepime. In Phase 1 studies, constipation and abdominal pain were reported. Additional risk information for VNRX-5133 and cefepime/VNRX-5133 are located in the VNRX-5133 IB.[1] The full risk profile for cefepime is described in the prescribing information for the product.

In nonclinical studies of VNRX-5133 alone, the kidney was determined to be a target organ of VNRX-5133 toxicity in both rats and dogs. In nonclinical studies of VNRX-5133 in combination with cefepime, there was no evidence of new or increased severity of toxicity in the combination-treated animals relative to animals treated with either drug alone based on clinical pathology, gross pathology, or histological parameters. No evidence of renal toxicity has been observed in Phase 1 studies of VNRX-5133 when administered alone or in combination of cefepime/VNRX-5133. Further information on nonclinical safety assessment and clinical safety is summarized in the IB.[1]

Meropenem is an approved medication with an established safety profile and will be administered at approved doses. Detailed information on the safety and risk profile of meropenem is provided in the package insert and SmPC.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of the study is to assess the efficacy of cefepime/VNRX-5133 compared with meropenem with respect to both per-patient microbiologic eradication and symptomatic resolution of all UTI-core symptoms (or return to pre-morbid baseline) at the Test of Cure (TOC) visit.

2.2 Secondary

The secondary objectives of the study are as follows:

- To determine the efficacy of cefepime/VNRX-5133 compared with meropenem with respect to the per-patient microbiological response, per-pathogen microbiologic response, and symptomatic resolution of all UTI-core symptoms at various timepoints in various populations

- To determine the efficacy of cefepime/VNRX-5133 compared with meropenem with respect to the per-patient microbiological response, per-pathogen microbiologic response, and symptomatic resolution of all UTI-core symptoms in patients with cUTI due to cefepime-resistant pathogens at various timepoints in various populations

- To evaluate the safety and tolerability profile of cefepime/VNRX-5133 compared with meropenem in the treatment of patients with a cUTI in the safety population

- To evaluate the steady-state PK of cefepime and VNRX-5133 in patients using a population PK model

3 STUDY PLAN

3.1 Study Design

Study VNRX-5133-201 is a Phase 3, randomized, multicenter, double-blind, double-dummy, active-controlled noninferiority study to evaluate the efficacy, safety, and tolerability of cefepime/VNRX-5133 compared with an active control, meropenem, in adult patients with cUTI, including AP. Each patient is expected to complete the study within approximately 4 to 5 weeks.

Patients with cUTI, including AP, will be enrolled. After obtaining signed informed consent and confirming eligibility within 24 hours prior to randomization, patients will be randomized in a 2:1 ratio to receive either cefepime/VNRX-5133 (2 g/0.5 g IV q8h) infused over 2 hours plus meropenem placebo infused over 30 minutes or the active comparator, meropenem (1 g IV q8h) infused over 30 minutes plus cefepime/VNRX-5133 placebo infused over 2 hours starting on Study Day 1.

Patients will be stratified by the type of infection (AP only versus complicated lower UTI with or without AP) and by region (North America and Western Europe versus Eastern Europe versus rest of the world). At least 30% of the population will have AP.

Patients may receive up to 24 hours of antibacterials for treatment of cUTI prior to randomization; however, the number of patients with prior antibacterial use will be limited to approximately 25% of the population. Before receipt of study drug, urine specimen and blood cultures will be obtained from all patients for culture and for *in vitro* antibacterial susceptibility testing. Patients with an indwelling catheter should have urine samples collected following the placement of a new catheter, or if the indwelling catheter cannot be removed, aseptic techniques should be used through a properly disinfected collection port. Patients with an indwelling catheter should be randomized only if they are expected to permanently discontinue use of the catheter prior to Study Day 5.

Screening assessments will also include a Daily Patient Symptom Questionnaire (DPSQ) and a Pre-morbid Patient Symptom Questionnaire (PPSQ). The DPSQ will be administered at screening, daily while on study drug, and at End of Treatment (EOT), TOC, and Late Follow-up (LFU) visits to determine the presence and intensity of cUTI symptoms. The PPSQ will be administered once at screening to determine whether a patient normally experiences urinary tract symptoms (i.e., in the absence of a UTI) that may be attributable to other disease processes (e.g., benign prostatic hyperplasia [BPH]).

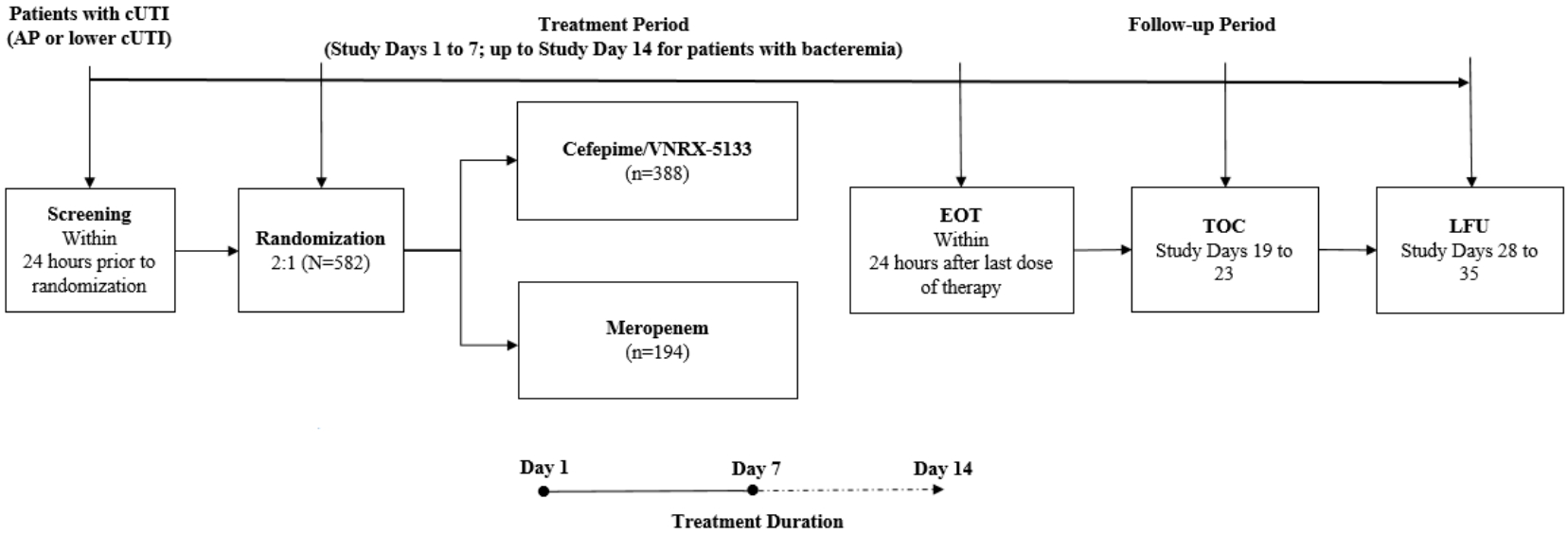
Study drug will be administered IV for 7 days and will be considered completed after the third dose on Study Day 7 for patients without bacteremia. All patients (who do not require dosing adjustments for renal dysfunction) will receive at least 19 doses. Patients without bacteremia will receive a maximum of 21 doses of active study drug. Patients with bacteremia at study entry may have their treatment extended up to 14 days at the investigator's discretion.

Patients will be admitted at screening and remain at the study site or hospital for the duration of the IV treatment period and through the EOT visit. The EOT visit will be performed within 24 hours after the last dose of IV study drug. Patients may be discharged from the study site after the EOT visit if clinically stable and at the investigator's discretion.

Patients must return to the study site for the TOC visit (Study Days 19 to 23) and the LFU visit (Study Days 28 to 35).

The study design is summarized in Figure 1.

Figure 1 Study Schematic



AP=acute pyelonephritis; cUTI=complicated urinary tract infection; EOT=End of Treatment; LFU=Late Follow-up; TOC=Test of Cure.

3.2 Study Endpoints

3.2.1 Primary

The primary endpoint is the demonstration of microbiological success (any gram negative bacterial pathogens found at study entry are eradicated to $<10^3$ colony forming units per milliliter [CFU/mL] on urine culture) and the demonstration of symptomatic clinical success (symptomatic resolution or return to pre-morbid baseline of all UTI-core symptoms including frequency, urgency, dysuria, suprapubic/pelvic pain, and flank pain, patient is alive, and patient has not received additional antibacterial therapy for cUTI) at TOC in the microbiological intent-to-treat (microITT) population.

3.2.2 Secondary

Clinical and Microbiological Efficacy:

- The proportion of patients with both microbiological success and symptomatic clinical success at TOC in the extended microITT population, clinically evaluable (CE)- TOC and microbiologically evaluable (ME)- TOC populations
- The proportion of patients with both microbiological success and symptomatic clinical success at EOT in the micro-ITT, ME-EOT and CE-EOT analysis populations and at LFU in the micro-ITT, ME-LFU and CE-LFU populations
- The proportion of patients with per-patient microbiological success at EOT, TOC and LFU in the micro-ITT, ME-EOT, ME-TOC and ME-LFU populations
- The proportion of patients with symptomatic clinical success at EOT, TOC and LFU in micro –ITT, CE- EOT, CE-TOC and CE-LFU populations
- The proportion of patients with clinical success based on investigator opinion at TOC in the microITT population
- The proportion of patients with per-pathogen microbiological success at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations
- The proportion of patients with both microbiological success and symptomatic clinical success among those with cefepime-resistant pathogens at EOT in the micro-ITT, ME-EOT and CE-EOT populations, TOC in the micro-ITT, ME-TOC, and CE-TOC populations, and at LFU in the micro-ITT, ME-LFU and CE-LFU populations
- The proportion of patients with per-patient microbiological success among those with cefepime-resistant pathogens at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations

- The proportion of patients with per-pathogen microbiological success among those with cefepime-resistant pathogens at EOT in the micro-ITT and ME-EOT populations, TOC in the micro-ITT and ME-TOC populations, and at LFU in the micro-ITT and ME-LFU populations

- The proportion of patients with symptomatic clinical success among those with cefepime-resistant pathogens at EOT in the micro-ITT and CE-EOT populations, TOC in the micro-ITT and CE-TOC populations, and at LFU in the micro-ITT and CE-LFU populations

Safety and Tolerability:

- Safety and tolerability will be assessed based on the incidence and severity of adverse events (AEs) and serious adverse events (SAEs), exposure, mortality, reasons for discontinuation of study drug and study withdrawal, vital sign measurements, and clinically significant changes in clinical chemistry, hematology, urinalysis, and coagulation laboratory values.

Pharmacokinetics:

- The population PK analysis using data from the study will be described in a population PK analysis plan and summarized in a separate report.

Resolution of Fever:

- The time to first defervescence (≤37.8°C) in the microITT population for patients who have fever (>38°C) at baseline will be assessed as an exploratory endpoint.

3.3 Schedule of Assessments

See Table 1 for general schedule of assessments and Table 10 for the schedule of PK assessments.

4 POPULATION

4.1 Number of Patients

A total of 582 adult male and female patients will be randomized into 2 groups in a 2:1 ratio (388 patients to cefepime/VNRX-5133; 194 patients to meropenem) at approximately 122 sites. The study duration will be approximately 14 months.

4.2 Inclusion Criteria

Patients must meet the following general inclusion criteria to be eligible for inclusion in the study:

1. Provide signed informed consent
2. Adult male and female, ≥18 years of age
3. If female, meets at least 1 of the following criteria:
   - Surgically sterile
   - Age ≥50 years and postmenopausal for ≥12 months
   - Age <50 years and postmenopausal for ≥2 years
   - Patient has a negative serum pregnancy test and agrees not to attempt pregnancy and, if participating in sexual activity, agrees to use an effective dual method of contraception
4. Patient has pyuria as demonstrated by at least 1 of the following:
   - Urine dipstick positive for leukocyte esterase
   - White blood cells (WBC) >10 cells/μL in unspun urine
   - WBC >10 cells per high power field (HPF) in urine sediment
5. Demonstrates either AP or complicated lower UTI as defined by the following criteria:
   a. AP is indicated by the presence of both of the following criteria:
      - At least 1 of the following is present:
        - Nausea or vomiting
        - Chills or rigors or warmth associated with fever, defined as body temperature >38°C
      - Has flank pain or costovertebral angle tenderness

b. Complicated lower UTI is indicated by the presence of all 3 of the following criteria:

- At least 1 of the following is present:
  - Nausea or vomiting
  - Chills or rigors or warmth associated with fever, defined as body temperature >38°C
- At least 1 of the following signs/symptoms is present:
  - Dysuria
  - Urinary urgency
  - Urinary frequency
  - Pelvic pain or suprapubic tenderness/pelvic tenderness
- At least 1 of the following complicating factors is present:
  - Chronic urinary retention
  - Obstructive uropathy (if complete obstruction, should intend to relieve obstruction within 48 hours after randomization)
  - Neurogenic bladder with presence or history of urine residual volume of >100 mL
  - Indwelling catheter (with expectation for permanent discontinuation of the catheter by Study Day 5)

6. Requires IV antibacterial therapy as initial treatment for cUTI

4.3 Exclusion Criteria

Patients who meet any of the following general exclusion criteria will not be eligible for inclusion in the study:

1. Receipt of effective antibacterial drug therapy for cUTI for a continuous duration of more than 24 hours during the previous 72 hours prior to randomization

2. Where a urine culture result is available:

- At least 1 uropathogen at $\geq 10^5$ CFU/mL is resistant to a meropenem, or
- A gram-negative bacterial pathogen is not identified
- More than 2 microorganisms are isolated regardless of the colony count, or
- The patient has a confirmed fungal UTI with colony count $\geq 10^3$ CFU/mL

3. Requirement for use of nonstudy systemic antibacterial drug therapy that would have a potential effect on outcome evaluations in patients with cUTI

4. Patients with suspected or confirmed prostatitis or urinary tract symptoms attributable to sexually transmitted disease

5. Patients with perinephric or renal abscess

6. Patients with renal transplantation or receiving hemodialysis or peritoneal dialysis

7. Patients with urinary diversions (e.g., ileal loops, cutaneous urostomy)

8. Patients who may need ongoing antibacterial drug prophylaxis after treatment of cUTI (such as vesico-ureteral reflux)

9. Any recent history of trauma to the pelvis or urinary tract

10. Patient has any urinary catheter or device or foreign body that will not be discontinued by Study Day 5, including, but not limited to, indwelling bladder catheter, urinary catheter, nephrostomy tubes, or stent

11. Patient is unlikely to respond to 7 days of antibacterial therapy for the treatment of cUTI without bacteremia or up to 14 days of therapy for treatment of cUTI with bacteremia

12. Patient has acute hepatitis, cirrhosis (Child-Pugh Class B or C), acute hepatic failure, or acute decompensation of chronic hepatic failure

13. Patient has had a heart, lung, heart-lung, or pancreatic transplant at any time; or bone marrow transplant in the preceding year

14. Patient has any of the following laboratory values:

- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease (MDRD) formula[2]
- Hematocrit <25% or hemoglobin <8 g/dL
- Platelet count <50,000/mm^3
- Total bilirubin >3.0× the upper limit of normal (ULN), unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert's disease
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0× ULN at screening. Patients with values >3.0× ULN and <5.0× ULN are eligible if these values are acute and documented as being directly related to the infectious process being treated.

- Alkaline phosphatase >3.0× ULN. Patients with values >3.0× ULN and <5.0× ULN are eligible if this value is acute and documented as being directly related to the infectious process being treated.

15. Patient has a history of serious hypersensitivity (e.g., anaphylaxis), serious allergy, or any serious reaction to cephalosporin, penicillin, carbapenem, or other β-lactam antibacterials

16. Patient is considered unlikely to survive the 4- to 5-week study period or have a rapidly progressive or terminal illness, including septic shock, that is associated with a high risk of mortality

17. Patient requires concomitant medication with valproic acid or divalproex

18. Patient is in a situation or has a condition that, in the investigator's opinion, may interfere with optimal participation in the study, or is unlikely to comply with protocol (e.g., inability to fully comprehend and clearly respond to questions on the PPSQ and DPSQ in a reliable manner, uncooperative attitude, inability to return for follow-up visit, or unlikely to complete the study)

19. Patient is participating in any other clinical study that involves the administration of an investigational product at the time of presentation or during the course of the study or has received treatment with an investigational product in the 30 days prior to study enrollment

20. Female patients who are pregnant, lactating, or planning to become pregnant during this study

4.4 Timing of Enrollment and Randomization

Assessments performed as part of routine standard of care prior to consent (e.g., blood culture, laboratory tests) may be used to satisfy screening requirements; however, no study-specific procedures may be performed prior to informed consent. The timing of enrollment (i.e., informed consent) and randomization of patients to receive study drug is presented in Table 1.

4.5 Patient Screening and Replacement

Patients who drop out or withdraw for any reason without completing all screening evaluations successfully or who fail to meet the inclusion and exclusion criteria will be considered "screening failures". Randomized patients who are withdrawn from the study will not be replaced.

Detailed discontinuation and withdrawal requirements and procedures are detailed in Section 6.3.

5 STUDY DRUG MANAGEMENT

5.1 Identity of Investigational Products

The investigational products for the study are detailed in Table 2.

Further details on investigational products, preparation, storage, and administration are provided in the pharmacy manual.

Table 2 Investigational Products

Drug Product	Dose Administered	Dosage Form
Meropenem	1 g IV q8h	1 g/vial
Cefepime	2 g IV q8h	2 g/vial
VNRX-5133	0.5 g IV q8h	0.5 g/vial
Meropenem placebo	Matching meropenem	Sodium chloride injection USP 0.9%
Cefepime/VNRX-5133 placebo	Matching cefepime/VNRX-5133	Sodium chloride injection USP 0.9%

IV=intravenous; q8h=every 8 hours; USP=United States Pharmacopeia.

5.1.1 Storage

VNRX-5133 drug product will be stored according to instructions in the pharmacy manual.

Cefepime and meropenem will be stored according to the manufacturer's recommendations in their respective package inserts.

5.1.2 Packaging and Shipment

VNRX-5133 drug product will be supplied as a sterile, white to yellow powder in single-dose vials.

Cefepime will be supplied as a sterile, white to pale yellow powder in single-dose vials.

Meropenem will be supplied as a sterile white to pale yellow powder in single-dose vials.

Sodium chloride (0.9% solution) used for study drug reconstitution and for placebo will be obtained.

5.2 Preparation of Study Drug

Study drug will be prepared by an unblinded pharmacist or designee as outlined in the pharmacy manual. Blinded study staff, including the investigator and blinded study site personnel, cannot participate in the preparation of study drug.

Meropenem (1 g/vial) will be reconstituted solution as described in the package insert.

For cefepime/VNRX-5133, cefepime hydrochloride (2 g/vial, sterile, white to pale yellow powder) and VNRX-5133 (0.5 g/vial sterile, white to yellow powder) will each be reconstituted independently, then combined into a single IV bag, and diluted with 0.9% sodium chloride solution.

For cefepime/VNRX-5133 placebo and meropenem placebo, 0.9% sodium chloride for injection will be used matching cefepime/VNRX-5133 and meropenem, respectively.

Details on the preparation of study drug and blinding of the prepared bags are provided in the pharmacy manual. Study drug and placebo IV bags as well as IV tubing will be blinded with sleeves.

5.3 Dose and Administration

Each patient will receive a 30-minute infusion and a 2-hour infusion q8h. If only 1 line is available for IV medication administration, the 30-minute infusion should be administered prior to the 2-hour infusion. The 30-minute and 2-hour infusions may be administered concurrently if 2 separate lines are used.

Patients randomized to cefepime/VNRX-5133 will receive meropenem placebo IV immediately followed by cefepime/VNRX-5133 (2 g/0.5 g IV q8h). Meropenem placebo will be administered via IV pump over 30 minutes. Cefepime/VNRX-5133 will be administered via IV pump over a 2-hour period.

Patients randomized to receive meropenem will also receive cefepime/VNRX-5133 placebo IV immediately following meropenem (1 g IV q8h). Meropenem will be infused over 30 minutes. Cefepime/VNRX-5133 placebo will be administered via IV pump over a 2-hour period.

Study drug administration for patients with normal renal function or mild renal impairment is presented in Figure 2. For patients with normal renal function or mild renal impairment with eGFR ≥60 mL/min/1.73 m^2, a 1-time adjustment of dose regimen for cefepime/VNRX-5133 or meropenem may be made after administration of the first dose to allow the patient to shift onto a hospital medication administration schedule. Their second dose may be administered as soon as 4 hours and as long as 10 hours after administration of the first dose. No other adjustments to cefepime/VNRX-5133 or meropenem may be made, except for patients with changes in eGFR as described in Section 5.3.2.

The date and time of each infusion (start and stop time of infusion) will be recorded. In the event that there is an issue with a patient's IV infusion site, the planned infusion may be paused to restart another IV. The stop and restart times must be recorded.

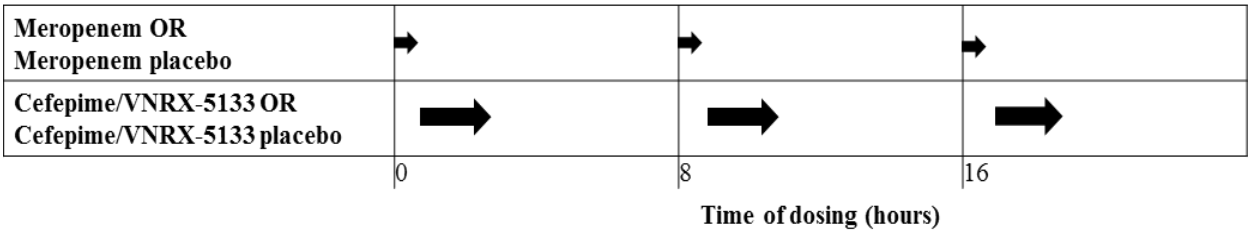
Dosing adjustments for cefepime/VNRX-5133 (or cefepime/VNRX-5133 placebo) and meropenem (or meropenem placebo) in patients with renal insufficiency are described in Section 5.3.2. The initial dose chosen should be based on the most recent eGFR value obtained prior to dosing. However, because dosing recommendations for the study drugs vary depending on the patient's renal function, the investigator should consider whether the change in eGFR warrants a change in IV study drug dosage or frequency. Since a decline in renal function may be

transient, eGFR should be closely followed in patients demonstrating renal dysfunction at any point before or during the study to ensure that therapeutic doses are being administered. In particular, when the eGFR falls between 50 and 60 mL/min/1.73 m^2 (at which point there are different dosing recommendations for cefepime/VNRX-5133 [or cefepime/VNRX-5133 placebo] and meropenem [or meropenem placebo]) or when eGFR falls below 30 mL/min/1.73 m^2 (at which point study drug should be discontinued), a repeat serum creatinine test result should be obtained, and eGFR calculation should be repeated before dose adjustments are made.

5.3.1 Dosing in Patients with Normal Renal Function or eGFR >60 mL/min/1.73 m^2

Study drug dosing in patients with normal renal function or mild renal impairment (eGFR >60 mL/min/1.73 m^2) is presented in Figure 2.

Figure 2 Study Drug Dosing in Patients with Normal Renal Function or eGFR >60 mL/min/1.73 m^2



eGFR=estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease.
Note: eGFR is calculated using the MDRD formula.

5.3.2 Dose Adjustment for Patients with eGFR ≤60 mL/min/1.73 m^2

When clinically indicated, eGFR calculation should be repeated to determine whether dose adjustment is needed. If the dose is adjusted, local clinical laboratory and eGFR results should be recorded on the unscheduled/local laboratory electronic case report form (eCRF).

The dose regimen of all study drugs should be adjusted according to the guidelines detailed in Table 3 based on eGFR. Given the different eGFR requirements for dose change across the treatment regiments, eGFR should be re-tested before adjusting therapy if the eGFR is between 50 and 60 mL/min/1.73 m^2. Similarly, eGFR should be re-tested before discontinuing therapy when the eGFR is <30 mL/min/1.73 m^2.

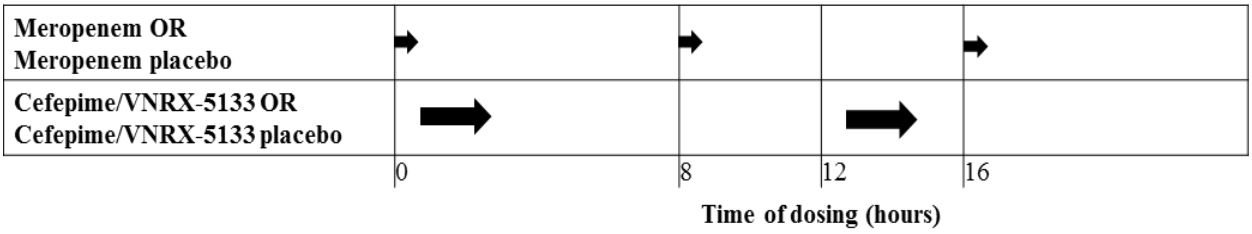
The adjusted dose regimens for patients based eGFR are also presented in Figure 3 and Figure 4.

Table 3 Dose Guidelines for Patients Based on Renal Function

eGFR[1] (mL/min/1.73 m^2)	Cefepime/VNRX-5133 or Cefepime/VNRX-5133 placebo	Meropenem or Meropenem placebo
>60	2 g/0.5 g IV q8h over 2 hours	1 g IV q8h over 30 minutes
>50-60	2 g/0.5 g IV q12h over 2 hours[2]	1 g IV q8h over 30 minutes[2]
30-50	2 g/0.5 g IV q12h over 2 hours	1 g IV q12h over 30 minutes
<30	Discontinue study drug[3]	Discontinue study drug[3]

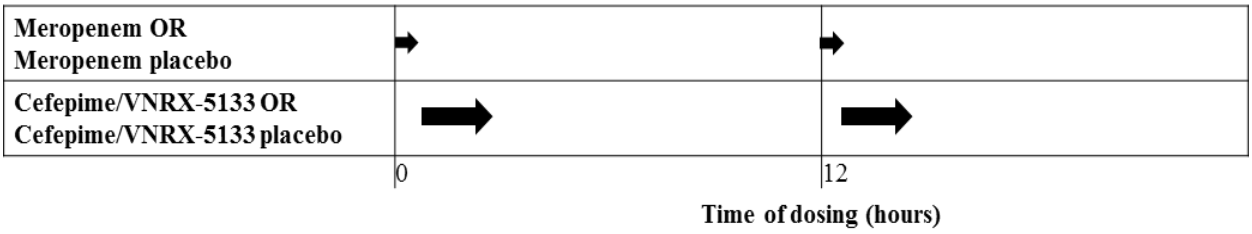
eGFR=estimated glomerular filtration rate; IV=intravenous; MDRD=Modification of Diet in Renal Disease; q8h=every 8 hours; q12h=every 12 hours.
1 eGFR is calculated using the MDRD formula.
2 Repeat serum creatinine test and recalculate eGFR. If eGFR remains >50 to 60 mL/min/1.73 m^2, adjust dose accordingly.
3 Repeat serum creatinine test and recalculate eGFR. If eGFR remains <30 mL/min/1.73 m^2, discontinue all study drug.

Figure 3 Study Drug Dosing in Patients with eGFR >50 to 60 mL/min/1.73 m^2



eGFR=estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease.
Note: eGFR is calculated using the MDRD formula.

Figure 4 Study Drug Dosing in Patients with eGFR 30 to 50 mL/min/1.73 m^2



eGFR=estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease.
Note: eGFR is calculated using the MDRD formula.

5.4 Treatment Duration

All patients will receive 7 days of IV treatment. Based on the scheduled study drug administration for patients without bacteremia, the patient could complete treatment on study day 7 or study day 8.

All non-bacteremic patients (who do not require dosing adjustments for renal dysfunction) will receive at least 19 doses and no more than 21 doses of study drug.

Patients with bacteremia at study entry may have their treatment extended up to 14 days at the investigator's discretion, but may complete therapy as early as Study Day 7 after their third dose.

There is no oral stepdown therapy, and patients are not permitted to continue oral antibacterials at home after completion of IV study drug (e.g. prophylaxis). If prophylactic therapy is warranted due to recurrent cUTIs, it should not be started until after the LFU visit if possible. Patients who are known to require prophylactic therapy and for whom withholding therapy until the LFU visit is not in their best interest should not be enrolled (see Exclusion Criterion 8). The Investigator should continually assess whether the study drug has failed (i.e., the patient has signs and symptoms of cUTI that have not improved or have recurred such that additional antibiotic therapy is warranted) and rescue therapy is required.

5.5 Accountability

Study drug will only be prepared by the unblinded pharmacist or designee. Study drug will be dispensed in a blinded manner to the investigator or medically qualified designated personnel by the unblinded pharmacist or designee. Study drug will only be administered to patients by medically qualified designated personnel who have been appropriately trained to administer study drug.

The unblinded pharmacist is responsible for the control of study drugs under investigation. Adequate records of the receipt and disposition of the study drug must be maintained. Drug disposition records must be kept current.

A separate unblinded study monitor will periodically review pharmacy logs and drug accountability. All records and drug supplies must be available for inspection by the study monitor at every monitoring visit. Any reconstituted unused study drug has to be inactivated, and unused, used, or partially used vials should be destroyed after use at the study site per local institute policy and procedures. If the study site does not have a destruction policy, the unused, used, or partially used vials can be shipped back to the depot for destruction. Completed drug dispensation records will be returned to the sponsor. The investigator's copy of the drug dispensation record(s) must accurately document the return of all study drug supplies to the depot, if applicable.

5.6 Treatment Compliance

All study drug will be administered by medically qualified designated personnel. To ensure treatment compliance, date, and exact start and stop times of study drug administration, including times for any interruptions that occur, will be recorded for all study drug administered in the eCRF by the investigator or authorized designee.

6 STUDY CONDUCT

All procedures will be performed in accordance with the schedule of assessments as detailed in Table 1. Detailed instructions for specific study procedures are provided in Section 7. Detailed requirements for reporting AEs and SAEs are provided in Section 8.

6.1 Enrollment and Randomization

After providing informed consent, patients will be enrolled into the study, entered into the Interactive Web Response System/Interactive Voice Response System (IWRS/IVRS), and assigned a unique screening number from the IWRS/IVRS for the screening process. After completing the screening process, patients who meet all eligibility criteria will be re-entered into the IWRS/IVRS and assigned a unique randomization number and study drug randomly computer-generated by the IWRS/IVRS. Randomization and screening numbers will not be reused. Patients will be randomly assigned to receive either cefepime/VNRX-5133 (2 g/0.5 g IV q8h) plus meropenem placebo, or the active comparator, meropenem (1 g IV q8h) plus cefepime/VNRX-5133 placebo, in a 2:1 ratio according to the randomization number. Randomization occurs after screening and prior to administration of the first dose of study drug. Administration of the first dose of study drug marks the start of Study Day 1. Therefore, randomization may occur on the same calendar day as Study Day 1 or on the previous calendar day.

Patients will be stratified by the type of infection (AP only versus complicated lower UTI with or without AP) and by region (North America and Western Europe versus Eastern Europe versus rest of the world). At least 30% of the population will have AP. Patients may receive up to 24 hours of antibacterial for treatment of cUTI prior to randomization; however, the number of patients with prior antibacterial use will be limited to approximately 25% of the population.

Patients who fail to meet the inclusion and exclusion criteria should not be randomized or receive study drug. There will be no exceptions to this rule. Patients who fail to meet the inclusion and exclusion criteria will not be rescreened. Procedures for ineligible patients who are erroneously randomized are described in Section 6.1.1.

6.1.1 Incorrectly Randomized Patients

The investigator should inform the sponsor or designee of patients who are randomized erroneously, do not meet the selection criteria, are incorrectly started on study drug, or who subsequently fail to meet the study criteria after treatment initiation. The patient should continue to receive study drug unless the investigator or sponsor considers that it is not in the best interest of the patient. The investigator should use their clinical discretion to determine whether discontinuation of study drug is warranted.

6.1.2 Blinding

All study drugs will be prepared at the study site by an unblinded pharmacist or designee. Prepared study drug and placebo IV bags and IV tubing will be blinded with sleeves to maintain the blind. To maintain blinding, the randomization code and study drug assignment will be provided by the IWRS/IVRS to the unblinded pharmacist or unblinded designee for dispensing

purposes and kept in the pharmacy, accessible to the unblinded pharmacist and designee only. The unblinded pharmacist or designee is not permitted to perform any other study procedures.

The sponsor, investigator, patient, and study site staff, with the exception of the unblinded pharmacist or designee, will remain blinded to study drug. The unblinded study monitor (separate from the other blinded monitors) will also remain unblinded.

The bioanalytical laboratory where the PK samples will be analyzed will be provided treatment assignment information to facilitate analyzing samples using methods for only treatments administered. A third party pharmacokineticist responsible for the PK analysis may be unblinded in order to begin analysis of data prior to study completion. This pharmacokineticist will have no involvement in the conduct of the study. No one else will have access to the treatment assignment information.

Procedures to maintain study blinding will be detailed in a separate blinding plan.

6.1.3 Unblinding

Unblinding of therapy assignment may be requested in an emergency if unblinding is considered necessary for medical management of the patient. In such case, the investigator is strongly encouraged to contact the medical monitor to discuss the case prior to unblinding; however, the decision and ability to unblind is independent of medical monitor's input.

If the data and safety monitoring board (DSMB) determines individual treatment assignment unblinding for patients is required to support an ad hoc meeting, an independent statistician will provide treatment information to the DSMB, and the DSMB will review unblinded data in the closed session.

6.2 Study Restrictions and Prohibitions

6.2.1 Restricted and Prohibited Medications

Use of systemic antibacterials other than study drug therapy, including prophylactic antibacterials, is not permitted during the study except in the following circumstances:

- If *Enterococcus* spp. or methicillin-resistant *Staphylococcus aureus* is isolated or suspected, then open-label vancomycin, linezolid, or daptomycin may be added to either of the study regimens according to the usual practice of the investigator.

- When the investigator considers addition of nonstudy antibacterials essential to the safety and well-being of the patient due to an AE (i.e., a new infection develops at another site). In this circumstance, if possible, the investigator should attempt to choose an antibacterial that will not have activity against the patient's baseline cUTI pathogen(s) to avoid confounding the assessment of the effect of study drug.

Patients who are known to require prophylactic therapy and for whom withholding therapy until LFU visit is not in their best interest should not be enrolled (see Exclusion Criterion 8).

Probenecid should not be administered. Probenecid may decrease excretion of β-lactam antibiotics.

Valproic acid and divalproex sodium should not be administered. Valproic acid concentrations in the blood may drop below the therapeutic range when co-administered with meropenem.

The following medications should be used with caution in all patients:

- Aminoglycosides: Concomitant administration of cefepime results in an increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibacterial drugs. Monitor renal function closely if aminoglycosides are administered

- Diuretic nephrotoxicity has been reported following concomitant administration of other cephalosporins with potent diuretics such as furosemide. Monitor renal function when cefepime is concomitantly administered with potent diuretics.

6.2.2 Contraception Requirements

Male patients who are not surgically sterilized and female patients of childbearing potential must agree to use an effective dual method of contraception during the study. A woman is considered of childbearing potential unless postmenopausal (age ≥50 years and ≥12 months without menses or age <50 years and ≥2 years without menses) or surgically sterilized. Male patients may not donate sperm from the first dose of study drug until 90 days after the last dose of study drug is administered.

6.2.3 Management of Indwelling Bladder Catheters

Indwelling bladder catheters that have been in place for >24 hours prior to screening must be removed or replaced prior to collection of urine at screening for urinalysis and culture (unless removal or replacement is considered unsafe or is contraindicated due to a recent procedure or urological condition), so that the urine culture results are an accurate representation of the pathogen(s) present.

Patients should only be enrolled if the indwelling bladder catheter is expected to be permanently discontinued prior to Study Day 5.

Indwelling bladder catheters should be maintained as a sterile, closed drainage system, and the junction of the catheter and drainage tube should not be disconnected. Besides permanent catheter discontinuation, other indications for indwelling bladder catheter change may include malfunction or leakage, obstruction, and contamination of the system (breakage between the catheter and drainage tube).

6.3 Premature Discontinuation

Patients are free to withdraw from the study or study drug at any time. Patients may also be prematurely discontinued from study drug or withdrawn from the study at the discretion of the investigator or sponsor at any time. Once a patient has been withdrawn from the study, they may

not be re-entered. Reasons for discontinuation from study drug or from the study will be collected in the eCRF.

6.3.1 Study Drug Discontinuation

Patients may be prematurely discontinued from study drug (i.e., before 7 full days of therapy and/or before cure of the infection [i.e., rescue therapy is necessary]) for the following reasons:

- Insufficient therapeutic effect of the study drug (i.e., requirement for additional nonstudy antibacterial therapy to treat cUTI based on the investigator's clinical judgement)
- AE
- Withdrawal by patient (the patient is free to discontinue therapy at any time)
- Physician decision (i.e., in the opinion of the investigator, it is not in the best interest of the patient to continue study drug)
- Sponsor decision
- A decrease in eGFR to <30 mL/min/1.73 m^2 (An eGFR <30 mL/min/1.73 m^2 should be rechecked and confirmed before discontinuation.)
- AST or ALT ≥10× ULN

If a patient is prematurely discontinued from study drug, the EOT visit should be performed, and every effort should be made to retain the patient in the study and perform all assessments at the TOC and LFU visits. Patients withdrawn from study drug should receive rescue therapy (if appropriate) as determined by the investigator.

6.3.2 Study Withdrawal

Participation in the study is strictly voluntary. A patient has the right to withdraw from the study at any time for any reason without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, the patient will be seen and assessed by the investigator at the time of withdrawal. If the patient has withdrawn from the study prior to completion of study therapy, every effort should be made to perform the EOT visit. AEs and SAEs will be followed up.

6.4 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

All deviations will be compiled in a centralized location.

Deviations will be classified by whether or not they meet the definition of important protocol deviations in a blinded manner. Important protocol deviations are a subset of deviations that

might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being.

Deviations will be categorized by type and will be reviewed on an ongoing basis. Protocol deviation notification and reports are submitted to regulatory authorities and/or relevant institutional review boards (IRBs) according to applicable requirements/guidelines/law.

6.5 Data Collection

All clinical data, including AEs and prior/concomitant medications, will be collected for each patient by an electronic data capture (EDC) system in an eCRF. Source data supporting EDC entries will be recorded in the patient's medical records according to the standard practice of the study site.

Investigators and study site personnel will be responsible for entering data within the eCRF and will respond to queries within the EDC system. Correction of any data errors and other such changes will be made within the EDC system and captured in the electronic audit trail.

7 DESCRIPTION OF STUDY PROCEDURES

Study procedures are specified in the general schedule of assessments in Table 1 and the schedule of PK assessments are presented in Table 10.

7.1 Screening

Screening assessments and procedures must be performed within 24 hours prior to randomization. The following assessments and procedures will be performed at screening:

- Obtain informed consent (see Section 4.4)
- Confirm eligibility (see Sections 4.2 and 4.3)
- Collect medical and surgical history (see Section 7.9.1)
- Collect demographics (see Section 7.9.1)
- Collect prior and concomitant medications (including prior antibiotic therapy) (see Section 7.9.2)
- Perform complete physical examination (see Section 7.9.3)
- Perform UTI-focused physical examination (see Section 7.9.3)
- Perform DPSQ (see Section 7.7.1)
- Perform PPSQ (see Section 7.7.1)
- Measure height and weight (see Section 7.9.4)
- Measure vital signs: blood pressure, heart rate, respiratory rate, and temperature (oral or tympanic) (see Section 7.8.1)
- Calculate eGFR (see Section 7.8.2)
- Perform 12-lead electrocardiogram (ECG; see Section 7.8.3)
- Obtain blood cultures (see Section 7.7.4.2)
- Obtain quantitative urine culture (see Section 7.7.4.1)
- Obtain urine microscopy or urine dipstick to document WBCs or leukocyte esterase, respectively (see Section 7.8.4)

- Perform serum or urine beta-human chorionic gonadotropin (β-hCG) test at a local laboratory site for women of childbearing potential to confirm eligibility (see Section 7.8.4)

- Obtain serum sample for β-hCG for women of childbearing potential and send to the central laboratory (see Section 7.8.4)

- Obtain blood and urine samples for central laboratory safety assessments (use local laboratory results to confirm eligibility; see Section 7.8.4)

- Monitor AEs (see Section 7.8.5)

Randomization marks the end of the screening/baseline period and the start of the treatment period.

7.2 Treatment Period

Randomized patients will receive study drug as described in Section 5. The duration of therapy for each patient in both treatment groups will be 7 days of IV therapy (see Section 5.4). Patients with bacteremia at study entry may have their treatment extended up to 14 days at the investigator's discretion.

Administration of the first dose of study drug marks the beginning of Study Day 1. Subsequent study days are based on calendar days.

Patients must remain hospitalized at the study site while receiving treatment. After the EOT visit, patients may be discharged at the investigator's discretion.

7.2.1 Study Day 1

Administration of the first dose of study drug marks the beginning of Study Day 1. The following assessments and procedures will be performed during Study Day 1 of the treatment period:

- Randomization (Note: Randomization occurs after screening and prior to administration of the first dose of study drug. It may occur on the same calendar day as Study Day 1 or on the previous calendar day; see Section 6.1)

- Review concomitant medications (see Section 7.9.2)

- Perform UTI-focused physical examination (Note: Does not need to be repeated on Study Day 1 if screening and Study Day 1 occur on the same calendar day; see Section 7.9.3)

- Perform DPSQ (Note: Does not need to be repeated on Study Day 1 if screening and Study Day 1 occur on the same calendar day; see Section 7.7.1)

- Measure vital signs: blood pressure, heart rate, respiratory rate, and temperature (oral or tympanic) (Note: Does not need to be repeated on Study Day 1 if screening and Study Day 1 occur on the same calendar day; see Section 7.8.1)
- Collect blood samples prior to the first dose of study drug for PK analysis (see Section 7.10)
- Monitor AEs (see Section 7.8.5)
- Administer study drug (see Section 5.3)

7.2.2 Study Days 2 to 7 (or up to Study Day 14 for Patients with Bacteremia)

The following assessments and procedures will be performed during Study Days 2 to 7 (or up to Study Day 14 for patients with bacteremia) of the treatment period:

- Review concomitant medications daily (see Section 7.9.2)
- Perform UTI-focused physical examination daily (see Section 7.9.3)
- Perform DPSQ daily (see Section 7.7.1)
- Measure vital signs: blood pressure, heart rate, respiratory rate, and temperature (oral or tympanic) daily (see Section 7.8.1)
- As clinically indicated: eGFR using serum creatinine results from local laboratory. Report eGFR if results are clinically significant or if results warrant a change in dose of study drug (see Section 7.8.2)
- On Study Days 2 and 3 only: collect blood samples for PK analysis (see Section 7.10)
- On Study Day 4 only: perform 12-lead ECG immediately after completion of study drug infusion and as clinically indicated (see Section 7.8.3)
- Obtain blood cultures if clinically indicated, or if a previous blood culture was positive, repeat blood cultures should be performed every 2 to 3 days until clearance of bacteremia is documented (see Section 7.7.4.2)
- On Study Day 4 and on Study Days 8 and 12 if still on IV study drug: obtain blood and urine samples for central laboratory safety assessments (see Section 7.8.4)
- Monitor AEs daily (see Section 7.8.5)
- Administer study drug daily (see Section 5.3)

7.3 End of Treatment Visit

The EOT visit will be performed within 24 hours after the last IV dose of study drug (i.e., on Study Day 7 or 8 for patients without bacteremia who complete a full course of therapy, or Study Days 7, 8, 9, 10, 11, 12, 13, 14, or 15 for patients with bacteremia [depending on the when the investigator determines treatment is complete]). Patients who discontinue treatment early should have the EOT visit performed within 24 hours of the last dose of IV study drug. Patients may be discharged from the study site after the EOT visit if clinically stable and at the investigator's discretion.

When EOT occurs on the same calendar day as the last day of IV therapy, any assessments already performed on that calendar day (see Section 7.2.2) do not need to be repeated, unless clinically indicated based on the investigator's judgement or in the event that EOT occurs on Study Day 1.

The following assessments and procedures will be performed at EOT:

- Review concomitant medications (see Section 7.9.2)
- Perform UTI-focused physical examination (see Section 7.9.3)
- Perform DPSQ (see Section 7.7.1)
- Measure vital signs: blood pressure, heart rate, respiratory rate, and temperature (oral or tympanic) (see Section 7.8.1)
- As clinically indicated: eGFR using serum creatinine results from local laboratory (see Section 7.8.2)
- Obtain blood cultures if clinically indicated, or if a previous blood culture was positive, repeat blood cultures should be performed every 2 to 3 days until clearance of bacteremia is documented (see Section 7.7.4.2)
- Obtain blood and urine samples for central laboratory safety assessments (see Section 7.8.4)
- Obtain quantitative urine culture (see Section 7.7.4.1)
- Determine Investigator Opinion of Clinical Response (see Section 7.7.5)
- Monitor AEs (see Section 7.8.5)

7.4 Test of Cure Visit

The TOC visit will be performed between Study Days 19 and 23. Patients who were discharged must return to the study site for the TOC visit.

The following assessments and procedures will be performed at TOC:

- Review concomitant medications (see Section 7.9.2)
- Perform UTI-focused physical examination (see Section 7.9.3)
- Perform DPSQ (see Section 7.7.1)
- Measure vital signs: blood pressure, heart rate, respiratory rate, and temperature (oral or tympanic) (see Section 7.8.1)
- As clinically indicated: calculate eGFR using serum creatinine results from local laboratory (see Section 7.8.2)
- Obtain blood cultures if clinically indicated, or if a previous blood culture was positive, repeat blood cultures should be performed every 2 to 3 days until clearance of bacteremia is documented (see Section 7.7.4.2)
- Obtain blood and urine samples for central laboratory safety assessments (see Section 7.8.4)
- Obtain quantitative urine culture (see Section 7.7.4.1)
- Determine Investigator Opinion of Clinical Response (see Section 7.7.5)
- Monitor AEs (see Section 7.8.5)

7.5 Late Follow-up Visit

The LFU visit will be performed between Study Days 28 and 35. Patients who were discharged must return to the study site for the LFU visit.

The following assessments and procedures will be performed at LFU:

- Review concomitant medications (see Section 7.9.2)
- Perform UTI-focused physical examination (see Section 7.9.3)
- Perform DPSQ (see Section 7.7.1)
- Measure vital signs: blood pressure, heart rate, respiratory rate, and temperature (oral or tympanic) (see Section 7.8.1)
- As clinically indicated: calculate eGFR using serum creatinine results from local laboratory (see Section 7.8.2)

- Obtain blood cultures if clinically indicated, or if a previous blood culture was positive, repeat blood cultures should be performed every 2 to 3 days until clearance of bacteremia is documented (see Section 7.7.4.2)
- Obtain blood and urine samples for central laboratory safety assessments (see Section 7.8.4)
- Obtain quantitative urine culture (see Section 7.7.4.1)
- Determine Investigator Opinion of Clinical Response (see Section 7.7.5)
- Monitor AEs (see Section 7.8.5)

7.6 Unscheduled Assessments

Unscheduled assessments may be conducted at any time according to the investigator's discretion, as clinically appropriate.

7.7 Efficacy Evaluations

7.7.1 Assessment of Symptomatic Clinical Response

The symptomatic clinical success at TOC is one of the components of the primary outcome of this study; responses at EOT and LFU are secondary endpoints.

During study conduct, patients will be required to report their cUTI symptoms on a series of formal questionnaires that will be administered by trained study center staff. The PPSQ will be administered once at screening to determine whether a patient normally experiences urinary tract symptoms (i.e., in the absence of a UTI) that may be attributable to other disease processes (e.g., BPH). The patients will be administered the DPSQ at screening, daily while on study drug, and at EOT, TOC, and LFU visits. The data collected from the questionnaires will be used to programmatically assess the symptomatic clinical response as defined in Table 4 and Table 5. Instructions for performing the PPSQ and DPSQ are detailed in Appendix 2.

The DPSQ should also be performed at any unscheduled visit occurring for any reason between the EOT and TOC visits and/or between the TOC and LFU visits.

Table 4 Symptomatic Clinical Response Criteria at EOT

Response Category	Definition
Symptomatic clinical success	All of the following have occurred: • Resolution (or return to pre-morbid state) of the core symptoms of cUTI (dysuria, frequency, urgency, suprapubic/pelvic pain, and flank pain) present at study entry • No new core cUTI symptoms have developed and no symptoms have worsened • Patient is alive
Symptomatic clinical failure	Occurrence of 1 or more of the following: • Confirmed persistence of at least 1 symptom (i.e., non-resolution or not having returned to pre-morbid state) of the core symptoms of cUTI (dysuria, frequency, urgency, suprapubic/pelvic pain, and flank pain) • Development of 1 or more core symptoms of cUTI not present at baseline • Death
Indeterminate symptomatic clinical response	Cases where the symptomatic clinical response could not be assessed

cUTI=complicated urinary tract infection; EOT=End of Treatment;

Table 5 Symptomatic Response Criteria at TOC and LFU

Response Category	Definition
Symptomatic clinical success	All of the following have occurred: • Resolution (or return to pre-morbid state) of the core symptoms of cUTI (dysuria, frequency, urgency, suprapubic/pelvic pain, and flank pain) present at study entry • No new core cUTI symptoms have developed and no symptoms have worsened • Patient is alive • Patient has not received additional antibiotics for the treatment of cUTI (other than those permitted per protocol) after EOT
Symptomatic clinical failure	Occurrence of 1 or more of the following: • Confirmed persistence of at least 1 symptom (i.e., non-resolution or not having returned to pre-morbid state) of the core symptoms of cUTI (dysuria, frequency, urgency, suprapubic/pelvic pain, and flank pain) • Development of 1 or more core symptoms of cUTI not present at baseline • Death • Patient has received additional antibiotics for the treatment of cUTI (other than those permitted per protocol) after EOT
Indeterminate symptomatic clinical response	Cases where the symptomatic clinical response could not be assessed

cUTI = complicated urinary tract infection; TOC= Test of Cure; LFU = Late Follow-up

A patient will be said to have symptomatic clinical relapse at the LFU visit if their symptomatic clinical response was success at the TOC visit and is failure at the LFU visit. Similarly, a patient will be said to have sustained symptomatic clinical success at the LFU visit if their symptomatic clinical response was success at the TOC visit and is success at the LFU visit.

7.7.2 Assessment of Microbiological Response

The microbiological response of per-patient eradication at the TOC visit in the microITT population is one of the components of the primary outcome. The per-pathogen microbiologic response in the microITT, ME population at the EOT, TOC, and LFU visits as well as the

per-patient microbiological response in the microITT population at EOT and LFU and in ME population at EOT, TOC, and LFU are secondary outcomes. Microbiological response will be assessed per-pathogen and per-patient according to the definitions below. Microbiological outcome per-patient is assessed in a blinded manner. It is based on outcome per-pathogen isolated at the initial visit (considered as causative) and on the isolation of pathogens during the course of treatment or the posttreatment period.

Each baseline pathogen will be categorized at EOT, TOC, and LFU visits according to the microbiological response criteria shown in Table 6.

Table 6 Microbiological Response Criteria

Microbiological Response	Definition
Eradication	Demonstration that the bacterial pathogen found at study entry ($\geq 10^5$ CFU/mL) is eradicated to $<10^3$ CFU/mL
Persistence	Demonstration that the bacterial pathogen found at study entry ($\geq 10^5$ CFU/mL) grows $\geq 10^3$ CFU/mL
Indeterminate microbiological response	Repeat cultures are not performed

CFU=colony forming unit.

For patients from whom more than 1 baseline pathogen is isolated, the overall per-patient microbiological response assessment will be favorable only if the microbiologic response assessment for each of the baseline pathogens is eradication.

A patient will be said to have microbiologic recurrence at the LFU visit if their response was eradication at the TOC visit and persistence at the LFU visit. Similarly, a patient will be said to have sustained eradication at the LFU visit if their response was eradication at the TOC visit and is eradication at the LFU visit.

Pathogens identified in blood will be assigned a per-pathogen microbiologic response. In instances of cUTI with bacteremia, a favorable outcome for a baseline pathogen will require a favorable microbiologic response from the urine sample as well as the blood.

7.7.3 Other Microbiological Outcomes

7.7.3.1 Emergent Infections

Pathogens first appearing after baseline in patients with a different baseline pathogen are categorized as described in Table 7 and will be considered separately from microbiological response.

Table 7 Emergent Infection Criteria

Emergent Infection	Definition
Superinfection	Isolation of a new pathogen(s) (other than the original baseline pathogen[s]) from urine during treatment with study drug that is accompanied by new or worsening signs and symptoms of infection requiring alternative antimicrobial therapy
New infection	Isolation of a new pathogen(s) (other than the original baseline pathogen[s]) from urine after completion of study drug that is accompanied by new or worsening signs and symptoms of infection requiring alternative antimicrobial therapy

7.7.3.2 Persistence with Increasing Minimal Inhibitory Concentration

In patients with persistence, MICs of study drugs against pathogens isolated at baseline will be compared to MICs of study drugs against postbaseline pathogens. An outcome of persistence with increasing MIC is indicated by the organism displaying a ≥4-fold higher MIC to study drug received in a urine or blood culture obtained at EOT or later compared to baseline.

7.7.4 Specimen Collection and Analysis

Detailed instructions for the collection, storage, and transport of specimens are provided in the laboratory manual.

7.7.4.1 Urine Specimen

An adequate urine specimen for microbiologic evaluation must be obtained and sent to the local laboratory for culture, identification, and *in vitro* antibacterial susceptibility testing per institutional operating procedures at screening prior to randomization and at EOT, TOC, and LFU visits.

Urine samples should not be obtained from urinary catheter bags. Acceptable methods of collection of urine for culture include the following:

- Midstream clean catch (straight catheterization using sterile technique is preferred for female patients)
- Straight catheterization using sterile technique
- Suprapubic specimen collection using sterile technique
- Whenever possible, urine specimens should not be obtained from indwelling bladder catheters. When necessary, urine specimens in patients with indwelling bladder catheters should be obtained by sterile aspiration through the catheter port or by puncturing the catheter tubing with a needle and syringe if a port is not present.

The urine specimen should be plated for culture within 2 hours from the collection time, if the specimen is kept at room temperature. Alternatively, these tests may be performed within 24 hours of collection if the specimen is stored at 2°C to 8°C before processing. Refer to the laboratory manual for specimen storage and handling instructions.

The specimens should be processed according to recognized methods[3, 4] and following the standard operating procedures (SOPs) of the clinical microbiology laboratory at each study site.

All isolates of uropathogens at $\geq 10^5$ CFU/mL from the screening cultures and isolates of gram-negative uropathogens at $\geq 10^3$ CFU/mL from subsequent (i.e., follow-up) urine cultures must be sent by local laboratory to the central laboratory, where pathogen identification will be confirmed, and further susceptibility testing and characterization will be performed. Urine samples from which more than 2 pathogens were isolated may be considered to represent contamination.

All cultured isolates should be kept by the local laboratory until the end of the study as described in the laboratory manual.

7.7.4.2 Blood Cultures

Blood samples for microscopic evaluation, culture, identification, and *in vitro* susceptibility testing will be collected at screening for all patients and processed at the local microbiology laboratory per institutional SOPs. Postbaseline, blood cultures will be performed as clinically indicated. For patients with positive baseline blood cultures, cultures will be repeated every 2 to 3 days until negative.

Two sets of blood cultures should be collected from 2 different sites for aerobic incubation and, if possible, anaerobic incubation (i.e., 4 tubes). Each bottle should be inoculated with 10 to 15 mL of blood for a total of 40 to 60 mL per collection. Ideally, at least 1 set of blood cultures should be obtained through a venipuncture. Details concerning the collection and processing of blood cultures are provided in the laboratory manual.

Isolated pathogens will be sent to the central microbiology laboratory where pathogen identification will be confirmed and further susceptibility testing and characterization will be performed. Bacteria not considered pathogens (i.e., contaminants) should not be sent to the central laboratory.

Blood specimens should be processed according to recognized methods for aerobic and anaerobic organisms (e.g., as found in Jorgensen JH and Pfaller MA, Manual of Clinical Microbiology[5]; Leber AL, Clinical Microbiology Procedures Handbook[6]) following the SOPs of the qualified clinical microbiology laboratory at each study site. Microscopic evaluation and culture of specimens will be performed by the qualified local laboratory, along with susceptibility testing of pathogens cultured from the specimens if such testing is consistent with standard procedures at the institution.

All cultured isolates should be kept by the local laboratory until the end of the study as described in the laboratory manual.

7.7.5 Investigator Opinion of Clinical Response

Based on the entirety of the patient's clinical course and current status, including an evaluation of signs and symptoms (including systemic and cUTI-specific symptoms), physical examination,

laboratory values, and general well-being, the investigator should provide an Investigator Opinion of Clinical Response at the EOT, TOC, and LFU visits according to the definitions listed in Table 8.

Table 8 Investigator Opinion of Clinical Response Criteria

Investigator Opinion of Clinical Response	Definition
Success	All or most pretherapy signs and symptoms of the index infection have improved or resolved such that no additional antibiotics[1] are required for treatment of the cUTI
Success with treatment for asymptomatic bacteriuria	All or most pretherapy signs and symptoms of the index infection have improved or resolved such that no additional antibiotics[1] are required; however, treatment of asymptomatic bacteriuria is prescribed based on the opinion of the investigator[2]
Failure	Patients who meet at least one of the following criteria: • Death related to cUTI • Persistence or progression of cUTI symptoms such that additional antibiotics for cUTI are required • Patient previously met criteria for failure (not applicable for the EOT visit)
Indeterminate	An assessment was not performed due to any of the following: • Death where cUTI was clearly non-contributory • Assessment was not performed (e.g., due to missed visit, withdrawal of consent, or loss to follow-up)

cUTI=complicated urinary tract infection; EOT=End of Treatment.
1 This does not include antibacterials that are permitted per protocol for patients with *Enterococcus* or methicillin-resistant *S aureus* infections.
2 According to guidelines in both Europe and the United States, treatment of asymptomatic bacteriuria (the presence of 1 or more species of bacteria growing in the urine irrespective of the presence of pyuria, in the absence of signs or symptoms attributable to UTI) is in most cases not beneficial and may be harmful. Based on standard of care and protocol restrictions surrounding use of additional antibiotics, patients in this trial should not receive additional antibiotic for asymptomatic bacteriuria. Additional therapy should only be given if signs and symptoms warrant ongoing treatment for symptomatic cUTI (i.e., based on their clinical course in the absence of microbiological data).

7.8 Safety Evaluations

Safety and tolerability assessments will consist of AEs, clinical laboratory, vital signs, and 12-lead ECG examinations. Assessments will be performed in accordance with the schedule of assessments (see Table 1).

7.8.1 Vital Signs

Vital signs will be collected at screening, daily while on study drug therapy, at EOT, TOC, and LFU visits.

Vital signs do not need to be repeated on Study Day 1 if screening and Study Day 1 occur on the same calendar day.

At EOT, assessments already performed on the same calendar day do not need to be repeated unless clinically indicated based on the investigator's judgement.

Vital signs include heart rate, respiratory rate, temperature (oral or tympanic), and blood pressure. If more than 1 set of vital signs is acquired on a given calendar day, record the highest temperature and the heart rate, respiratory rate, and blood pressure associated with that temperature (or those acquired nearest to that temperature). Systolic and diastolic blood pressure and heart rate will be recorded after the patient has been resting for at least 5 minutes in the supine position. These assessments should made using an automated device.

Vital signs should also be performed at any unscheduled visit occurring for any reason between the EOT and TOC visits and/or between the TOC and LFU visits.

7.8.2 Estimated Glomerular Filtration Rate

The eGFR will be calculated at screening to determine eligibility and appropriate dosing of study drug using local laboratory serum creatinine results using the MDRD formula.[2] If the investigator determines that calculation of eGFR is warranted postbaseline (e.g., due to change in clinical status and/or for evaluation of need for dose change), local laboratory serum creatinine should be used and the results reported as an unscheduled laboratory test. An eGFR will also be calculated by the central laboratory using central blood results.

Calculation of eGFR is detailed below:

$$eGFR=175 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times 0.742 \text{ [if female]} \times 1.212 \text{ [if black]}$$

Note: The ethinicity factor should only be used for African Americans and should not be used with black patients of all other nationalities.

where S_{cr} is serum creatinine in mg/dL and eGFR is measured in mL/min/1.73m^2.

7.8.3 Electrocardiogram

A standard 12-lead ECG will be recorded after the patient has been resting for at least 5 minutes in the supine position. Safety ECGs should be reviewed by a medically qualified designated personnel at the site.

Baseline ECGs will be performed at screening. Study Day 4 ECGs will be collected immediately after completion of the cefepime/VNRX-5133 or cefepime/VNRX-5133 placebo infusion. Additional ECGs can be performed for safety reasons at any time as clinically indicated at the discretion of the investigator. Abnormalities should be followed up by the investigator. Copies of the ECGs should be kept as source documents.

7.8.4 Clinical Laboratory Tests

All blood and urine specimens will be sent to a central reference laboratory for analysis and testing. Blood and urine samples will be obtained during screening, on Study Days 4 and Study Days 8 and 12 if on IV treatment, and at EOT, TOC, and LFU visits. At screening, blood and

urine specimens will also be sent to a local laboratory to confirm eligibility for randomization. In the event that baseline central laboratory results are not consistent with eligibility criteria, the site will be asked to document the screening local laboratory result on a local laboratory result eCRF.

The procedures for the collection, handling, and shipping of testing samples are based on the central laboratory SOPs and are specified in the laboratory manual(s) provided to the study site.

All laboratory assessments listed in Table 9 will be performed on all samples at screening or baseline, during and post treatment, except for procedures used for screening purposes only. Baseline values will be obtained at screening.

Additional unscheduled samples may be collected at any time.

Table 9 Central Laboratory Assessments

Panel	Parameter(s)
Coagulation	Prothrombin time PTT INR
Chemistry	ALT Albumin Alkaline phosphatase AST Bicarbonate Bilirubin, total, direct, and indirect BUN Calcium Chloride CK Creatinine Glucose (nonfasting) LDH Potassium Phosphorus Protein, total Sodium
Hematology	Hematocrit Hemoglobin Platelet count RBC count WBC count with differential
Urinalysis	Urinalysis (appearance, bilirubin, glucose, ketones, leukocyte esterase, nitrite, pH, protein specific gravity, urobilirubin)

Panel	Parameter(s)
	Microscopy[1]
Pregnancy testing[2]	Serum β-hCG

β-hCG=beta-human chorionic gonadotropin; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CK=creatine kinase; INR=international normalized ratio; LDH=lactate dehydrogenase; PTT=partial thromboplastin time; RBC=red blood cell; WBC=white blood cell.

Note: Local laboratory results should be used at screening to confirm eligibility for randomization.
1 Microscopy should include assessment of WBCs, RBCs, casts, crystals, bacteria, and yeast.
2 Serum β-hCG must be performed as part of screening/eligibility in women of childbearing potential. However, a patient may begin study drug on the basis of a negative urine β-hCG, but a serum β-hCG test must still be obtained for confirmation.

7.8.5 Adverse Event Monitoring

AEs, including SAEs, will be collected from the time of informed consent through the last study visit. AEs that are ongoing at the LFU visit or at study withdrawal should be monitored until resolution, stabilization with sequelae, or death.

Definitions and procedures for AE and SAE reporting are detailed in Section 8. Other reportable events, though not considered AEs, should be reported as discussed in Section 9.

7.9 Other Assessments

7.9.1 Medical History and Demographics

A complete history to include medical and surgical history during the prior 5 years, as well as any other medical/surgical history relevant to the diagnosis of cUTI and/or participation in this study, and demographics (i.e., age, sex, ethnicity, and race) will be obtained at screening. Events occurring prior to the time of informed consent will be recorded as medical history.

7.9.2 Prior and Concomitant Medication Collection

Prior medications are defined as any prescription medication, over-the-counter medication, herbal supplement, and traditional medicines taken by the patient before randomization. All prior medications, including antimicrobials, taken during the 2 weeks prior to randomization will be collected at screening.

Concomitant medications are defined as any prescription medication, over-the-counter medication, herbal supplement, or traditional medicines taken by the patient after randomization. All concomitant medication, including antibacterials, will be collected from the time of randomization through the last study visit. Saline and similar volume replacers are not required to be recorded as a concomitant medication.

7.9.3 Physical Examination

A complete physical examination will be performed at screening consisting of general appearance, skin/subcutaneous tissue, head, ears, nose, throat, neck and thyroid, thorax, lungs,

cardiovascular, lymph nodes, abdomen, musculoskeletal, and neurological examinations. Genitalia, anus/rectal, and breast examinations will only be performed if medically indicated.

UTI-focused physical examinations, including assessment of costovertebral angle tenderness and suprapubic/pelvic tenderness, will be performed during screening, daily while on IV therapy at EOT, TOC, and LFU visits.

A UTI-focused examination should also be performed at any unscheduled visit occurring for any reason between the EOT and TOC visits and/or between the TOC and LFU visits.

7.9.4 Height and Weight Measurement

Height and weight measurement will be performed at screening.

7.9.5 Radiographic Examination

Radiographic imaging including X-ray imaging, ultrasonography, computed tomography, positron emission tomography, and magnetic resonance imaging scan is not required for this study, but may be performed at the investigator's discretion at any time as clinically appropriate. Results of any radiologic tests performed that are clinically relevant to the cUTI or an SAE should be recorded for all patients.

7.9.6 Surgical Procedures and Other Non-pharmacological Interventions

Any patient planning to undergo surgical treatment not compatible with the aims of the study must not be enrolled. For patients who need to undergo an unplanned surgical procedure during the study, the reason for the surgery must be documented as an AE in the eCRF.

Other non-pharmacological procedures that occur during the study will be entered into the eCRF including the date and reason for treatment/procedure.

7.10 Pharmacokinetics

Sparse plasma sampling for population PK analysis will be performed in all patients on Study Days 1, 2, and 3.

PK blood samples will be taken via an indwelling IV catheter or by direct venipuncture into dipotassium ethylenediaminetetraacetic acid (K_2-EDTA)-containing tubes. To ensure that accurate PK samples are obtained, the IV infusion site used for study drug administration must not be used for collection of blood for PK assessments, and it should not be drawn from the same arm as the line used for infusion.

PK blood samples should be taken relative to the start/end of the 2-hour infusion of cefepime/VNRX-5133 or placebo. Samples will be collected around the scheduled sampling time within the specified collection windows. The sites are encouraged to vary the sampling within the collection windows, at times convenient for the collection. The exact dates and times of blood sampling will be recorded in the eCRF.

Details on PK sample collection, handling, storage, and shipping are described in the laboratory manual. Time windows for PK assessments are presented in Table 10.

Table 10 Time Windows for Pharmacokinetic Assessments

Study Day	Scheduled Sampling Time	Collection Window
Study Day 1	Predose	Prior to initiation of study drug, within 3 hours prior to the first dose of study drug
Study Day 2	Predose	Within 30 minutes prior to the morning dose of study drug
Study Day 3	Predose	Within 30 minutes prior to the morning dose of study drug
Study Day 3	During infusion	Between 30 and 90 minutes after the start of infusion, and prior to the end of infusion
Study Day 3	End of infusion	Immediately after the infusion to within 30 minutes after the completion of the infusion
Study Day 3	2 hours after the end of infusion	Between 1 and 3 hours after the end of infusion
Study Day 3	4 hours after the end of infusion	Between 3 and 5 hours after the end of infusion
Study Day 3	6 hours after the end of infusion	Between 5 hours after the end of infusion and prior to the start of the next infusion

Note: After collection of the Study Day 3 predose sample, other Study Day 3 samples can be collected after any of the infusions on Study Day 3.

PK samples will only be assayed for patients randomized to receive cefepime/VNRX-5133.

All PK blood samples will be processed and assayed for VNRX-5133 and cefepime using validated assays. The steady-state PK of VNRX-5133 and cefepime will be determined in this patient population. Intrinsic and extrinsic factors will be explored in the population PK analysis. Population PK analysis methods will be described in a separate population PK analysis plan that will be finalized before the clinical database lock.

7.11 Pharmacogenomics

Pharmacogenomics analysis will not be performed.

7.12 Biomarkers

Assessment of biomarkers will not be performed.

7.13 Total Volume of Blood

Table 11 presents the number and approximate volume of blood samples and the total volume of blood that will be collected during the study.

If deemed necessary by the investigator or the sponsor, the number and/or volume of blood samples per assessment may be modified as long as the total volume of blood drawn for a patient does not surpass 500 mL (except when extra blood samples need to be taken for safety reasons).

Table 11 Total Blood Volume Collected

Assessment	Sample Volume (mL)	Total Number of Samples	Total Volume (mL)
Clinical chemistry	5	5 to 7	25 to 35
Hematology	3	5 to 7	15 to 21
Coagulation	4.5	5 to 7	22.5 to 31.5
Serum β-hCG	8.5	1	8.5
Blood culture[1]	10 to 15/vial, 40 to 60/culture (4 vials)	1	40 to 60
PK sampling	4	8	32
Total (approximate)		**25 to 31**	**143 to 188**

β-hCG=beta-human chorionic gonadotropin; PK=pharmacokinetic(s).

1 Four vials (10 to 15 mL/vial) will be collected for each blood culture collection. All patients will have 4 vials of blood collected at screening; additional blood culture samples will be collected only as clinically indicated or every 2 to 3 days until blood has cleared for patients with bacteremia at baseline.

7.14 Handling, Storage, Transport, and Destruction of Specimens

Detailed instructions for the handling, storage, transport, and destruction of biological specimens are provided in the laboratory manual.

7.14.1 Future Use of Stored Specimens

Blood, urine, and microbiological specimens remaining after safety and/or efficacy assessments are performed will not be stored for future use. A backup sample of each isolated pathogen (not specimen) from urine or blood that is shipped to the central microbiology laboratory must be retained at the local laboratory in case the central laboratory or the sponsor requests that it is to be shipped to the central laboratory for reanalysis.

Blood specimens remaining after PK assessments are performed will be stored for possible future drug metabolism and PK analyses.

No genetic or biomarker analysis will be performed.

8 ADVERSE EVENT ASSESSMENT AND REPORTING

8.1 Definition of an Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE definitions will be followed as stated in the "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (International Council on Harmonisation [ICH] topic E2A).[7]

8.1.1 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, on the basis of medical and scientific judgment, has any of the following characteristics:

- Results in death
- Is life-threatening (This refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization for a medical reason or prolongation of existing hospitalization (This refers to hospital admission required for treatment of the AE. Note: this does not include confinement in, for example, a respite unit, a skilled nursing unit, rehabilitation facility, the clinical research unit, or confinement due to planned or unplanned reason unrelated to study)
- Is a congenital anomaly/birth defect
- Is a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is an important medical event (Note: important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious)

The intensity and causality of SAEs will be determined as described in Section 8.3.1 and Section 8.3.2, respectively.

8.2 Documenting Adverse Events

All AEs and SAEs encountered during the clinical study will be reported in detail in the source documents and documented in the eCRF from the time of consent until completion of the LFU visit.

Events occurring over the previous 5 years prior to the time of informed consent will be recorded as medical and surgical history. Any medical occurrences that are new or worsened from the time of informed consent and up to and including the last study visit must be reported as AEs and SAEs.

Whenever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be reported. Each AE or SAE reported will be assessed for intensity. The date and time of onset, time relationship to dosing, and duration and outcome of each event will be noted.

Information to be collected for AEs includes event description, date of onset, assessment of severity and relationship to study product, and date of resolution of the event, seriousness, and outcome. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed until resolution, stabilization with sequelae, or death.

8.2.1 Reporting Serious Adverse Events

SAEs will be collected from the time of informed consent through the last study visit. SAEs that are ongoing at the time of the LFU visit will be followed until resolution, stabilization with sequelae, or death. SAEs that begin after the patient's participation in the study is complete, but that the investigator considers to be related to study drug, should be reported.

The investigator or study site personnel should notify the appropriate sponsor/contract research organization (CRO) pharmacovigilance representatives of all SAEs, regardless of relationship to study drug, within 24 hours of becoming aware of the event. The investigator or study site personnel will provide the initial notification by completing the SAE page in the eCRF, which must include the investigator's assessment of the relationship of the event to study drug and must be signed by the investigator. There may be situations in which minimal information is available. However, it is very important that the investigator always makes an assessment of causality. The investigator may change his/her assessment of the causality based on follow-up information and should amend the SAE report form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Covance Pharmacovigilance will forward SAE queries directly to the investigator requesting additional information. It is the investigator's responsibility to be diligent in providing this information as soon as it is available.

If an event meets serious criteria and it is not possible to access the EDC, the SAE should be submitted electronically using this email address: SAEintake@covance.com. If email access is

not available, the SAE may be reported telephonically using the following regional telephone numbers:

- Europe: +44 1628 540028
- North America: +1 888 887 8097
- Latin America: +1 609 419 2609
- Asia Pacific: +61 2 9888 8322

8.3 Assessment of Adverse Events

8.3.1 Assessment of Intensity

The severity of AEs will be assessed as mild, moderate, or severe according to the criteria below:

- Mild: patient has awareness of signs or symptoms, but they are easily tolerated and of minor irritant type causing no loss of time from normal activities. Symptoms do not require treatment or medical evaluation; signs and symptoms are transient.
- Moderate: event introduces a low level of inconvenience or concern to the patient and may interfere with daily activities but is usually improved by simple therapeutic measures; the event may cause some interference with functioning.
- Severe: event interrupts the patient's normal daily activities and generally requires systemic drug therapy or other treatment; the event may be incapacitating.

It is emphasized that the term severe is a measure of severity: thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe but may not be clinically serious.

8.3.2 Assessment of Causality

The investigator will assess the causal relationship between study drug and each AE and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?"

8.4 Adverse Event Follow-up

Follow-up of AEs will continue until resolution, stabilization with sequelae, or death. In case of ongoing AEs at the moment of database lock, the data obtained at the moment of database lock will be used in the statistical analysis.

8.5 Adverse Events of Special Interest

There are currently no AEs of special interest.

8.6 Exemptions from Adverse Event Reporting

8.6.1 Laboratory Abnormalities

Laboratory abnormalities should be reported as adverse events if the result is considered to be clinically significant by the investigator. Clinically significant abnormal clinical laboratory findings or other abnormal assessments that are associated with the disease being studied (unless judged by the investigator as more severe than expected for the patient's condition) or that are present or detected at the start of the study and do not worsen, will not be reported as AEs.

8.6.2 Disease Progression and Lack of Effect

Disease progression or deterioration of the patient's condition due to lack of improvement or worsening of the cUTI may or may not reflect failure of the study drug. Insufficient therapeutic effect will be captured as an efficacy outcome. Therefore, clinical and microbiological failures should not be reported as an AE. Furthermore, any event or extended hospitalization that is unequivocally due to disease progression should not be reported as an SAE unless it is believed that study drug actively contributed to the progression of the disease (i.e., not by way of insufficient therapeutic effect). Events that are a direct result of progression of the cUTI that progress to death will not be reported as SAEs but will instead be reported on a separate death form.

9 OTHER REPORTABLE EVENTS

9.1 Abnormal Liver Enzymes

The investigator is responsible for notifying the sponsor or sponsor representative within 24 hours of becoming aware of either of the following findings based on local or central laboratory testing results:

- AST or ALT ≥3× ULN and total bilirubin ≥2× ULN, OR
- ALT or AST ≥10× ULN

In cases meeting either of the above criteria (based on central or local laboratory results), the investigator must complete the liver enzyme eCRF. Appendix 3 describes the recommended diagnostic test that should be considered. If any diagnostic testing is performed, the results should be reported in the eCRF. Liver laboratory results should be followed locally over several days until resolution or stabilization of the laboratory abnormalities and should be documented in the local laboratory eCRF.

If a nonserious or serious AE is associated with the laboratory abnormalities, it should be reported separately as described in Section 8.

9.2 Overdose

Overdose is defined as administration of more than the intended dose in any given infusion of study drug or more than 4 infusions of study drug in a given 24-hour period. Any instance of overdose (suspected or confirmed) must be communicated to the sponsor or a specified designee within 24 hours and be fully documented. Overdose is not necessarily an AE, but if the consequences of the overdose result in a serious or nonserious AE, they should be reported as such, separate from the overdose. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

9.3 Pregnancy Reporting

A female clinical study patient may no longer receive the study drug and must immediately inform the investigator if she becomes pregnant during the study. Monitoring of the patient should continue until the outcome of the pregnancy is known.

The investigator should report all pregnancies of female clinical study patients or partners of male patients to the sponsor within 24 hours of becoming aware of them. The investigator should report all pregnancies to the IRB/independent ethics committee (IEC).

If written consent is obtained from the pregnant partner, monitoring of the partner should continue until the outcome of the pregnancy is known.

10 STATISTICS

10.1 General Procedures

Continuous clinical variables will be summarized descriptively (i.e., patient count, mean, standard deviation, minimum, median, and maximum). Categorical data will be summarized descriptively with frequencies and percentages based on the number of patients exposed within a treatment. Full details of the analysis will be described in the statistical analysis plan.

For the evaluation of clinical and microbiological response, missing data will be classified as indeterminate. Further details will be provided for the handling of all missing data in the statistical analysis plan.

10.2 Sample Size

The study will randomize 582 patients with cUTI into 2 groups in a 2:1 ratio (388 patients to cefepime/VNRX-5133; 194 patients to meropenem) at multiple study sites worldwide. Approximately 30% or more of patients should be diagnosed with AP. Randomization at study entry will be stratified by the type of infection (AP only versus complicated lower UTI with or without AP) and by region (North America and Western Europe versus Eastern Europe versus rest of the world). Patients with prior antibacterial use for cUTI will be limited to approximately 25% of the study population.

This sample size will provide at least 264 cefepime/VNRX-5133 patients and 132 meropenem patients for the primary comparisons of interest, based on an anticipated evaluability rate of 68%, a response rate of 75%, 90% power, a 2-sided alpha of 0.05, and a noninferiority margin of 15%.

10.3 Statistical Methods

10.3.1 Study Population

Study endpoints will be presented in the following populations:

- Intent-to-treat (ITT) population: all randomized patients
- microITT population: all patients randomized to treatment AND
    - Had a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a gram-negative pathogens against which both cefepime/VNRX-5133 and meropenem have antibacterial activity AND
    - Had no more than 2 microorganisms identified in the study entry culture regardless of colony count
- Extended microITT population: all patients randomized to treatment AND

- Had a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a gram-negative pathogen against which at least 1 study drug (i.e., cefepime/VNRX-5133 and/or meropenem) have antibacterial activity AND
- Had no more than 2 microorganisms identified in the study entry culture regardless of colony count

- CE-EOT, CE-TOC, and CE-LFU populations: all patients who meet the definition for the ITT population AND
  - Had an appropriate diagnosis of cUTI
  - Received treatment for ≥48 hours (or <48 hours if discontinued due to an AE or death)
  - Were evaluated for the appropriate endpoint at the relevant timepoint (i.e., EOT, TOC, and LFU) with an outcome that is not indeterminate
  - Did not violate entry criterion surrounding use of prior antibacterials
  - Did not receive a concomitant systemic antibiotic with potential activity against any of the baseline pathogens between the time of randomization and EOT, TOC, and LFU, respectively, except therapies used to treat cUTI in patients who have failed study drug
  - Did not have other confounding factors that interfered with the assessment of outcome as assessed by a blinded evaluability team prior to database lock
- ME-EOT, ME-TOC, and ME-LFU populations: all patients who meet the criteria for the microITT population AND
  - Both study drugs are known to have antibacterial activity against the baseline gram-negative pathogens AND
  - Had an appropriate diagnosis of cUTI
  - Received treatment for ≥48 hours (or <48 hours if discontinued due to an AE or death)
  - Were evaluated at the respective EOT, TOC, and LFU visits with a microbiological response of eradication or persistence (i.e., per-patient microbiologic response of success or failure)
  - Did not violate entry criterion surrounding use of prior antibacterials
  - Did not receive a concomitant systemic antibiotic with the potential activity against any of the baseline pathogens between the time of randomization and EOT, TOC,

and LFU, respectively, except therapies used to treat cUTI in patients who have failed study drug

- Did not have other confounding factors that interfered with the assessment of outcome as assessed by a blinded evaluability team prior to database lock

- Safety population: all patients who receive any dose of study drug

10.3.2 Demographic and Baseline Characteristics

Demographic and baseline data will be summarized for each dose group with descriptive statistics as detailed in Section 10.1. Enrollment, protocol deviations, and discontinuations from the study drug and the study will be summarized by treatment group. Demographics (age, race, ethnicity, and sex) and baseline characteristics such as medical history, baseline pathogen, renal function category, and presence of bacteremia will also be summarized by treatment group.

10.3.3 Signs and Symptoms

Signs and symptoms including frequency, urgency, dysuria, suprapubic/pelvic pain, and flank pain will be summarized for each dose group at each timepoint with descriptive statistics as detailed in Section 10.1.

10.3.4 Primary Endpoint

The primary clinical efficacy endpoint in this study is the proportion of cUTI patients with microbiological and symptomatic clinical success at TOC in the microITT population.

The aim of the analysis is to demonstrate that cefepime/VNRX-5133 is noninferior to meropenem with respect to this primary endpoint.

The response rate will be calculated for each treatment group as the number of successes divided by the total number of patients (success + failure + indeterminate). The difference in response rates between treatments (VNRX-5133 minus meropenem) will be presented along with a 95% confidence interval (CI), calculated using the method of Miettinen and Nurminen.[8] If the lower limit of the 95% CI for the difference in response is greater than or equal to the noninferiority margin of -15%, noninferiority will be declared. Further, if noninferority is concluded a test for superiority will be conducted. In this case, if the lower limit of the 95% CI for the difference in response is greater than or equal to zero superiority will be concluded.

A sensitivity analyses stratified by the the pre-specified stratification factors will also be performed for the primary endpoint. In addition, a sensitivity analysis will be performed which will define any additional antibacterial therapy given for cUTI as a symptomatic clinical failure.

10.3.5 Secondary Endpoints

The secondary clinical and microbiological efficacy endpoints are detailed in Section 3.2.2.

Cefepime-resistant pathogen endpoints will be analyzed in the same way as described for the primary endpoint (see Section 10.3.4) and secondary (clinical, per-patient and per-pathogen microbiological response) endpoints. Other by-pathogen data presentations will be summarized by frequency counts but not analyzed.

Additional analyses including sensitivity analyses using other visits or other poulations will be specified in the SAP.

10.3.6 Analysis of Safety

All safety analyses will be conducted in the safety population and will be summarized by treatment received.

Safety and tolerability will be assessed based on the incidence and severity of AEs and SAEs, exposure, mortality, reasons for discontinuation of study drug and study withdrawal, vital sign measurements, and clinically significant changes in clinical chemistry, hematology, urinalysis, and coagulation laboratory values.

Mortality rates will be presented by treatment group.

10.3.6.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an AE that occurs during or after treatment through the last study visit.

The incidence of TEAEs and SAEs will be summarized by treatment, by treatment and relationship, and by treatment and severity. The incidence will be presented by system organ class (SOC) and preferred term (PT); SOC, PT, and relationship to study drug administration; and SOC, PT, and severity. Tables of any TEAE resulting discontinuation of study drug and SAEs will also be provided.

10.3.6.2 Clinical Laboratory Evaluations

Clinical laboratory data (i.e., clinical chemistry, hematology, urinalysis, and coagulation parameters) will be listed and summarized by assessment and by timepoint including the actual value and change from baseline, and parameters outside the reference range will be noted. The number and percent of patients with treatment-emergent potentially clinically significant (PCS) laboratory values will be tabulated for each treatment group. PCS will be defined based on pre-specified criteria outlined in the statistical analysis plan. Plots of laboratory values versus time for key laboratory parameters will also be provided.

Liver enzymes will be classified as >3×, >5×, and >10× ULN, and the number and percentage of patients with any postbaseline value in one of the categories will be presented by treatment group.

10.3.6.3 Vital Signs

Descriptive statistics of vital sign measurements will be presented by treatment group and study assessment, as well as the change from baseline at each study visit.

10.3.6.4 Exposure

Exposure to study drug is defined as administration of any amount of study drug. The number of days of treatment and the total dose of treatment received per patient will be summarized.

Enrollment and withdrawals from the study and from study drug will be summarized by treatment group.

10.3.7 Analysis of Pharmacokinetics

The population PK analysis methods using data from the study will be described in a population PK analysis plan that will be finalized before clinical database lock. The population PK analysis plan will describe the analysis population, methods, and reporting for the population PK analysis. The population PK modeling will be summarized in a separate report.

10.3.8 Resolution of Fever

The time to first defervescence (≤37.8°C) in the microITT population for patients who have fever (>38°C) at baseline will be assessed as an exploratory endpoint.

The time to first defervescence will be assessed for patients in the specified study populations who have fever (>38ºC) at baseline, where defervescence (≤37.8ºC) is defined as the absence of fever based on the highest temperature recorded on each study day.

Time to first defervescence data will be summarized as the mean, median, minimum, and maximum number of days and number of patients. Data will also be presented as the frequency of patients achieving defervescence by day for each study day.

10.4 Interim Analysis

There are no plans for a formal interim analysis for efficacy.

Interim safety data will be reviewed by the independent DSMB as described in Section 11.2.

11 ETHICS AND RESPONSIBILITIES

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments through 2013.[9]

This study is also designed to comply with the ICH E6 Guideline for Good Clinical Practice (GCP) (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95)[10] and any

applicable national and local laws and regulations (e.g., Code of Federal Regulations Title 21, Parts 11, 50, 54, 56, 312, and 314, and Title 45 Part 46).

Guidelines adopted by the ICH and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate local law.

The investigator will be responsible for the care of the patients throughout the study. If the investigator is not present at the study site, he will leave instructions for the study site personnel and a telephone number where the investigator can be reached.

The investigator will be responsible for the medical follow up of patients.

11.1 Good Clinical Practice

This study will be carried out in accordance with GCP as required by the applicable national and local laws and regulations.

11.2 Data and Safety Monitoring Board

An independent DSMB will be formed to monitor interim safety data during the study. Procedures for DSMB reviews/meetings will be defined in the DSMB charter. The DSMB will review applicable data at scheduled timepoints during the study as defined in the charter.

Additional data may be requested by the DSMB. The DSMB will review grouped and unblinded data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study drug administration, and to continue, modify, or terminate this study.

11.3 Institutional Review Board/Independent Ethics Committee

The protocol and the Informed Consent Form (ICF) will be submitted for review and approval by an IRB/IEC prior to the eligibility screening. The composition of the IRB/IEC will be in accordance with applicable national and local laws and regulations and the recommendations of the ICH E6 Guideline for GCP.[10]

The CRO and/or clinical site personnel will keep the IRB/IEC informed regarding the progress of the study. All pregnancies will be reported to the IRB/IEC. All changes in research activities and all unanticipated problems involving risks to human patients will be immediately reported to the IRB/IEC. The study may be suspended pending further review by the IRB/IEC, except insofar as suspension would jeopardize the patient's health.

No changes will be made in the study without IRB/IEC approval, except when required to eliminate apparent immediate hazards to human patients (see Section 13).

Notification of the end of the study will be sent to the IRB/IEC within 90 days after completion of follow-up for the last patient. In case a study is ended prematurely, the IRB/IEC will be notified within 15 days, including the reasons for the premature termination. A summary of the

results of the study will be sent to the competent authority and the IRB/IEC within 1 year after the end of the study. The end of the study is defined as the date of receipt of the last data point for statistical analysis of the last patient participating in the study.

11.4 Informed Consent

All patients will be informed verbally and in writing regarding the objectives, procedures, and risks of study participation. Patients will have the opportunity to ask questions regarding the study and any information in the consent document before signing. For patients who are unable to provide informed consent, the investigator must obtain informed consent from the patient's legally authorized representative in accordance with applicable law.

The written consent document will embody the elements of informed consent as described in applicable national and local laws and regulations and will adhere to the ICH Harmonized Tripartite Guideline for GCP.[10] Informed consent will be obtained in accordance with applicable national and local laws and regulations, prior to performing any protocol-specified procedures or interventions.

Patients will be provided copies of the signed and dated consent form and any amendments.

Original consent forms will be kept on file by the investigator and made available if requested, by regulatory authorities, the sponsor, and/or other Quality Compliance representatives.

11.5 Records Management

The data management team is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality control, will comply with international regulatory guidelines, including ICH-GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in a data management plan. The data management plan will be written by the CRO and finalized prior to performing any data validation.

11.6 Source Documentation

All data will be collected on source documents and then entered in the eCRFs.

11.7 Study Files and Record Retention

All documents concerning the study will be kept on file in the central archives for at least 15 years after conduct of the study.

12 AUDITING AND MONITORING

Site monitoring is conducted to ensure that the human patient protection, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet ICH-GCP guidelines, when appropriate, and sponsor's regulatory guidelines. Site visits may be conducted by an authorized representative of the sponsor or regulatory agencies to inspect study data, patients' medical records, and eCRFs in accordance with ICH guidelines, GCP, and the respective local and national government regulations and guidelines.

The clinical research site will be monitored by a sponsor-approved study monitor to ensure correct performance of the study procedures and assure that the study will be conducted according to the relevant regulatory requirements. The eCRF entries will be verified with the source documentation.

A separate unblinded study monitor will periodically review pharmacy logs and drug accountability. Procedures to maintain study blinding will be detailed in the blinding plan.

12.1 Clinical Monitoring Plan

During study conduct, the sponsor or its designee will conduct periodic monitoring visits in accordance with a separate clinical monitoring plan to ensure that the protocol and GCPs are being followed. The monitors will review source documents to confirm that the data recorded on eCRFs are accurate. The investigator and institution will allow sponsor representatives, monitors, or its designee direct access to source documents to perform this verification.

It is important that the investigator and relevant personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Quality Control and Assurance

The study may be audited to assess adherence to the clinical study protocol and quality system. During the conduct of the study, process related audits may be performed. An audit certificate will be provided in the appendices of the final clinical study report (CSR) outlining any audits and other related activities performed.

The sponsor (or a designee) may conduct site audits.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed at the study site for all documents that are generated in relation with the study.

The study site will generate and implement a study-specific plan describing routine quality control and quality assurance activities for assessing the quality of the study data, protections of human patients, compliance with applicable federal regulations, and ICH E6 GCP guidelines.[10] The investigator will ensure all study site personnel are appropriately trained and applicable documentations are maintained on site. Study site monitors will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the

protocol, GCP, and the applicable regulatory requirements. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in a data management plan.

13 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by the sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. The sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, CRO, and/or the sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

14 STUDY REPORT AND PUBLICATIONS

The data generated by this study are confidential information of the sponsor. By signing the study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the sponsor. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

If an investigator or study site is to be included as an author of a publication manuscript prepared by the sponsor, the sponsor will allow the investigator or study site an adequate time for full review of the manuscript before publication.

The sponsor is responsible for preparing and providing the appropriate regulatory authorities with CSRs according to the applicable regulatory requirements. The sponsor's publication policy is discussed in the investigator's clinical research agreement.

15 STUDY DISCONTINUATION

Both the sponsor and the investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, the sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the investigator will inform the IRB/IEC of the same. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

16 CONFIDENTIALITY

Patient confidentiality is held strictly in trust by the participating investigator, study site personnel, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating patients. Study documents will be secured to maintain patient confidentiality.

All personal details of patients will be treated as confidential by the investigator and study site personnel, and handling of personal data will comply with applicable national and local laws and regulations.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval from the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect any documents maintained by the investigator, such as available medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

17 REFERENCES

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3. Jorgensen JH, Pfaller MA, eds. Manual of Clinical Microbiology. 11th ed. Washington, DC: ASM Press; 2015.
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8. Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985;4:213–26.
9. WMA Declaration of Helsinki (18th WMA General Assembly 1964), revised at 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013.
10. ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E6: Guideline for Good Clinical Practice (CPMP/ICH/135/95), January 1997.

18 APPENDICES

APPENDIX 1. CONTACT INFORMATION

Sponsor:	VenatoRx Pharmaceuticals, Inc. (VenatoRx) [redacted]
Sponsor Medical Representative:	[redacted] VenatoRx Pharmaceuticals, Inc. (VenatoRx) [redacted]
Medical Monitor:	[redacted] Covance Inc. [redacted]

APPENDIX 2. PATIENT SYMPTOM ASSESSMENT QUESTIONNAIRES

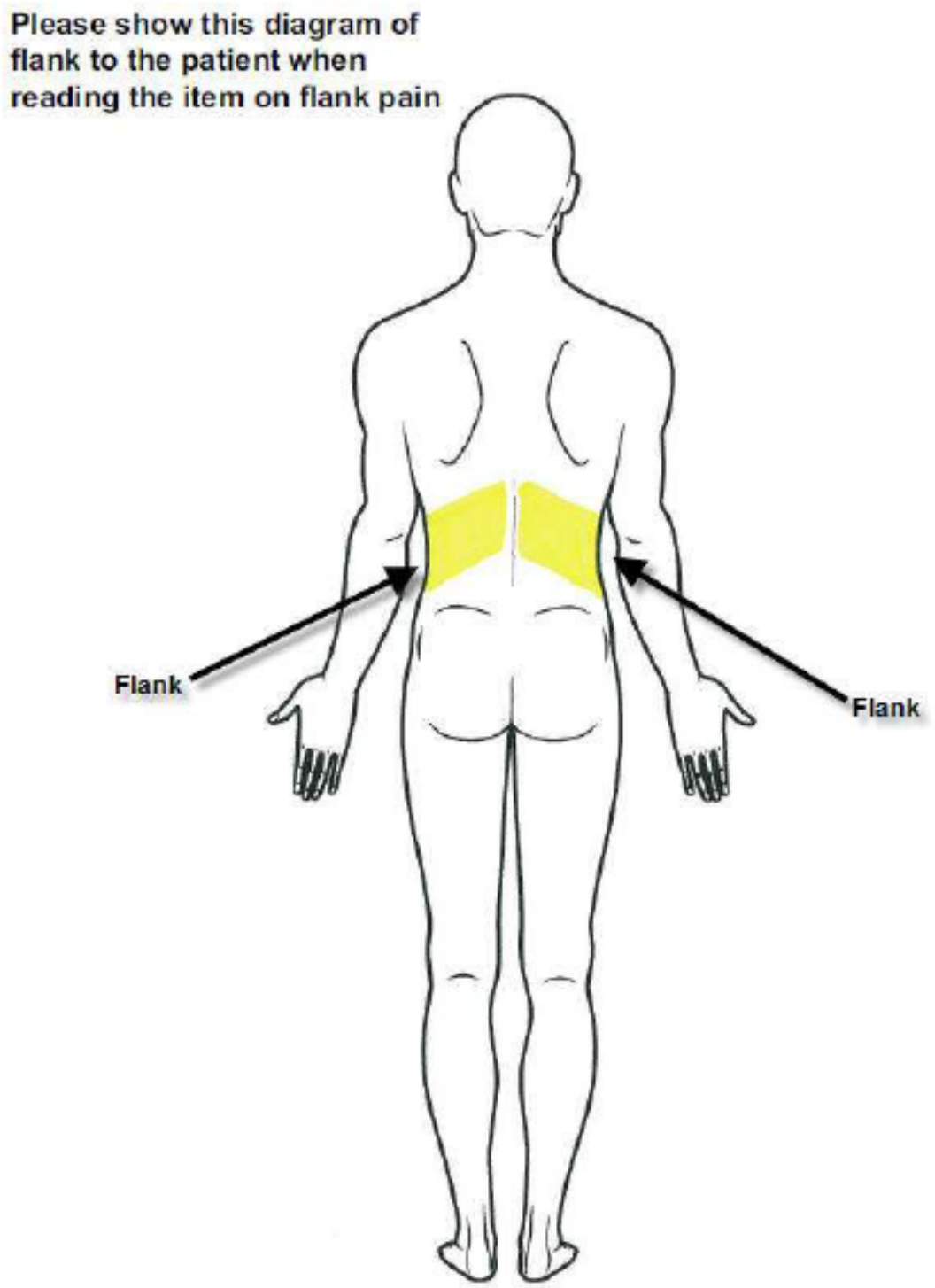
Interviewer Instructions for Administering Questionnaires

A standardized procedure for the administration of the patient symptom assessment questionnaires will be applied at every site to minimize bias. Please read these instructions carefully before administering the questionnaires and follow them exactly while administering it to your patient.

The Pre-morbid Patient Symptom Questionnaire (PPSQ) and the Daily Patient Symptom Questionnaire (DPSQ) should be administered according to the timepoints detailed in the schedule of assessments.

- Use a quiet place where the patient can be interviewed alone without interference from family or other staff members.
- Read the questionnaire instructions out-loud to the patient exactly as written.
- Read each item in the questionnaire and the response options to each item out-loud to the patient exactly as written.
- Read each item out-loud to the patient in the order provided in the questionnaire.
- Instruct patients to choose only 1 response for each item, and record the response selected by the patient.
- Show the diagram of the flank to the patient when reading the item on flank pain (see Figure 5).
- Repeat the instructions, questions, and response options to the patient, but do not interpret the questions for the patient, attempt to further explain the questions to the patient, or comment on the patient response.

Figure 5 Diagram of the Flank



Note: Location of flank on patient is indicated in yellow.

Pre-morbid Patient Symptom Questionnaire (PPSQ)

Patient number	
Date	
Time	

Instructions to Read to the Patient:

This questionnaire asks about symptoms you might be suffering from due to your current urinary tract infection. Some symptoms that we will ask about can be caused by health problems other than a urinary tract infection. That's why we want to know what you experience when you do not have a urinary tract infection.

You may have some of these symptoms when you don't have a urinary tract infection. In some cases, you may have some of these symptoms, but they could have gotten worse with your urinary tract infection.

Please respond whether you have had any of the following symptoms before the start of your current urinary tract infection started and how severe those symptoms were. In other words, tell us whether you have any of these symptoms when you are not suffering from a urinary tract infection.

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.

Symptom	No Symptoms	Mild	Moderate	Severe
Back pain—specifically flank pain (show the figure indicating flank area to the patient)				
Pain or discomfort in the lower abdomen or pelvic area				
Pain or burning when passing urine				
Urinating very often or frequency of urination				
A strong and uncontrollable urge to pass urine or urgency of urination				

Daily Patient Symptom Questionnaire

Patient number	
Date	
Time	

Instructions to Read to the Patient:

This questionnaire asks you about your symptoms in the past 24 hours. Please respond whether you have had the following symptoms or problems in the past 24 hours and how severe they were.

Answer each question by selecting only one response from the following possible options: no symptoms, mild symptoms, moderate symptoms, or severe symptoms.

Symptom	No Symptoms	Mild	Moderate	Severe
Back pain—specifically flank pain (show the figure indicating flank area to the patient)				
Pain or discomfort in the lower abdomen or pelvic area				
Pain or burning when passing urine				
Urinating very often or frequency of urination				
A strong and uncontrollable urge to pass urine or urgency of urination				

APPENDIX 3. RECOMMENDED LABORATORY TESTING IN PATIENTS WITH ELEVATED LIVER ENZYMES

The investigator is responsible for notifying the sponsor or sponsor representative within 24 hours of becoming aware of either of the following based on local or central laboratory testing results:

- AST or ALT ≥3× ULN and total bilirubin ≥2× ULN, OR
- AST or ALT ≥10× ULN

When the investigator indicates that either of these criteria have been met in the EDC system (Medidata/RAVE™), an automatic notification will be sent to the Covance PV & DSS team.

In all cases, the investigator should:

- Assess the patient for risk factors for liver enzyme abnormalities (e.g., heavy alcohol use, history of intravenous drug use, hypertriglyceridemia, history of hepatitis B or C infection, other)
- Evaluate for signs and symptoms of liver disease, including fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, or rash
- Re-evaluate liver enzymes (AST, ALT, alkaline phosphatase, and bilirubin [total, direct, and indirect]) at a local laboratory until resolution or stabilization. The suggested frequency is approximately every 24 to 48 hours until enzyme abnormalities have improved and less often thereafter until resolution or stabilization. The local laboratory results should be documented in the local laboratory eCRF.

In addition, the following recommended diagnostic tests may be considered:

Hepatitis A (IgG, IgM)	Antinuclear antibodies
Hepatitis B (HBsAb, HBcAb, HBeAg, HBsAg, HBV DNA)	Antimitochondrial antibodies
Hepatitis C (HCV Ab, HCV RNA)	Iron studies (serum iron, serum ferritin, total iron binding capacity, transferrin saturation)
Cytomegalovirus serology	Liver ultrasound
Epstein-Barr virus serology	

DNA=deoxyribonucleic acid; HBcAb=hepatitis B core antibody; HBeAg=hepatitis B e antigen; HBsAb=hepatitis B; HBsAg=hepatitis B surface antibody; HBV=hepatitis B virus; HCV Ab=hepatitis C virus antibody; HCV RNA=hepatitis C virus ribonucleic acid; Ig=immunoglobulin.