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

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STATISTICAL ANALYSIS PLAN

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STUDY NUMBER:	VNRX-5133-201
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[redacted] 03-Feb-22

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CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Acute pyelonephritis
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BPH	Benign prostatic hyperplasia
CE	Clinically evaluable
CE-EOT	Clinically Evaluable at End-of-Treatment
CE-LFU	Clinically Evaluable at Late Follow Up
CE-TOC	Clinically Evaluable at Test-of-Cure
CFU	Colony forming unit
CI	Confidence interval
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
eCrCl	Estimated creatinine clearance
eGFR	Estimated Glomerular Filtration Rate
ECMAP	Evaluation of clinical and microbiology assessment plan
ECMRT	Evaluation and clinical/microbiology review team
EmicroITT	Extended Microbiological Intent-to-Treat
EMA	European Medicines Agency
EOT	End of Treatment

ESBL	Extended spectrum beta-lactamase
FDA	US Food and Drug Administration
ITT	Intent-to-treat
IV	Intravenous(ly)
IVRS / IWRS	Interactive Voice Response System / Interactive Web Response System
LFU	Late Follow-up
MDR	Multidrug resistant
MDRD	Modification of diet in renal disease
ME	Microbiologically evaluable
ME-EOT	Microbiologically Evaluable at End-of-Treatment
ME-LFU	Microbiologically Evaluable at Late Follow Up
ME-TOC	Microbiologically Evaluable at Test-of-Cure
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimal inhibitory concentration
MicroITT	Microbiological intent-to-treat
MRSA	Methicillin resistant Staphylococcus aureus
MSSA	Methicillin susceptible Staphylococcus aureus
PCS	Potentially Clinically Significant
PK	Pharmacokinetic(s)
PPSQ	Pre-morbid Patient Symptom Questionnaire
PT	Preferred term
q8h	every 8 hours
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System organ class

TEAE	Treatment-emergent adverse event
TOC	Test of Cure
ULN	Upper limit of normal
UTI	Urinary tract infection
VNRX	Venatorx Pharmaceuticals, Inc. (Venatorx)

1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned summary and analysis of clinical data from the study, "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".

The study has been designed to address global regulatory requirements, and this SAP addresses the analyses to be performed for both EMA and FDA.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be identified herein. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the clinical study report (CSR). Any substantial deviations from this SAP will be clearly documented.

Changes made to the SAP after it has been signed but prior to database lock will be documented in an amendment. Any important changes made to the analysis after database lock will be described in the CSR.

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

2.0 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 a complicated urinary tract infection (cUTI), including acute pyelonephritis (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). Complicated urinary tract infection (cUTI) is the same as complicated lower UTI with or without AP for the purposes of the SAP. 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), Test of Cure (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).

3.0 STUDY OBJECTIVES

3.1 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 microbiological eradication and symptomatic resolution of all UTI-core symptoms (or return to pre-morbid baseline) at the Test of Cure (TOC) visit.

The primary objective refers to per-patient microbiological eradication. Although eradication is used to define per-pathogen outcomes, "per-patient microbiological eradication" is considered the same as per-patient microbiological success for the purposes of this SAP.

3.2 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 microbiological response, and symptomatic resolution of all UTI-core symptoms at various timepoints in various analysis populations.

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

in patients with cUTI due to cefepime-resistant pathogens at the Test of Cure (TOC) visit in various analysis 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 analysis population

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

4.0 ANALYSIS POPULATIONS

4.1 Intent-to-Treat Analysis Population (ITT)

The ITT analysis population will consist of all randomized patients regardless of whether the patient received study drug. A patient is considered randomized when a randomization number has been assigned.

4.2 Microbiological ITT (microITT) Analysis Population

The microITT analysis population will consist of all patients in the ITT analysis population and

- Had a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a gram-negative pathogen(s) 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

Antibacterial activity for meropenem is defined as Susceptible [S], or Intermediate [I], for Enterobacteriaceae and Susceptible [S] or Intermediate [I] for *P. aeruginosa* according to 2019 CLSI criteria[1]. For cefepime/VNRX-5133, 'antibacterial activity' is defined for Enterobacteriaceae as provisionally susceptible (MIC≤16 µg/mL); for *P. aeruginosa*, 'antibacterial activity' is also defined as provisionally susceptible (MIC≤16 µg/mL).

Table 1 Antibacterial activity of study drugs as defined by Minimum Inhibitory Concentration (MIC) against Enterobacteriaceae and P. aeruginosa

	MIC (µg/mL) corresponding to antibacterial activity	
Study drug	Enterobacteriaceae[a]	*P. aeruginosa*
Meropenem	≤2	≤4
Cefepime/VNRX-5133	≤16	≤16

[a]Due to changes in nomenclature, Enterobacteriaceae is the same as Enterobacterales for the purposes of this analysis.

For patients with two gram-negative baseline pathogens, both study drugs must have antibacterial activity against both pathogens.

4.3 Extended microITT Analysis Population

The extended microITT analysis population will consist of all patients in the ITT analysis population 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 species of microorganisms identified in the study entry culture regardless of colony count.

Antibacterial activity for meropenem and cefepime/VNRX-5133 is defined as outlined in Section 4.2.

4.4 Clinically Evaluable (CE) Analysis Populations

Three CE analysis populations will be defined, the CE-EOT, CE-TOC and CE-LFU analysis populations. The CE analysis populations will consist of all patients included in the ITT analysis population who also meet the criteria listed below. These criteria will be programmed from the database and/or be reviewed manually by the Sponsor in a blinded manner prior to database lock to confirm each patient's inclusion in the CE analysis populations.

Details regarding the programming and review of electronic case report form (eCRF) data and the database to establish inclusion in the CE analysis populations will be included in the micro and clinical/microbiological assessment plan (ECMAP).

- 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 a response that is not indeterminate and within the protocol defined windows

- 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 and clinical/microbiological review team (ECMRT) prior to database lock. This includes but is not limited to unblinding events.

4.5 Microbiologically Evaluable (ME) Analysis Populations

Three ME analysis populations will be defined, the ME-EOT, ME-TOC and ME-LFU analysis populations. The ME analysis populations will consist of all patients included the microITT analysis population who also meet the criteria listed below. These criteria will be programmed from the database and/or be reviewed manually by the Sponsor in a blinded manner prior to database lock to confirm each patient's inclusion in the ME analysis populations.

Details regarding the programming and review of CRF data and the database to establish inclusion in the ME analysis populations will be included in the ECMAP.

- Both study drugs are known to have antibacterial activity against all baseline gram-negative pathogens (antibacterial activity as defined above) 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 (ie, per-patient microbiological response of success or failure) and within the protocol defined windows
- 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 ECMRT prior to database lock. This includes but is not limited to unblinding events.

4.6 Safety Analysis Population

The Safety analysis population will consist of all patients who receive any dose of study drug. Data will be presented based upon the study drug actually received. All safety analyses will be conducted in this analysis population.

5.0 ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is the demonstration of microbiological success (all gram-negative bacterial pathogens found at baseline are eradicated to $<10^3$ colony forming units per milliliter [CFU/mL] on urine culture post-baseline) 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 has not received additional antibacterial for cUTI) at TOC in the microbiological intent-to-treat (microITT) analysis population.

Patients with missing data such that a symptomatic clinical and/or microbiological response cannot be determined will be considered an indeterminate response. Since the analysis of the primary endpoint is based on the microITT Analysis Population, patients with an indeterminate response are considered non-responders. For the microITT analysis population, the proportion of microITT patients considered responders is defined using the following formula (where the denominator is comprised of the total number of patients in the microITT analysis population):

$$\frac{\text{Number of patients who are responders}}{\text{(Number of patients who are responders + Number of patients who are non-responders + Number of patients who have an indeterminate response)}}$$

The various scenarios of microbiological response and symptomatic clinical response will result in an overall response as outlined in Table 2. Additional details regarding definition of symptomatic clinical and microbiological response are provided in Section 5.2.1 and 5.2.3.

Table 2 Definition of overall response for the primary endpoint of Per-Patient Microbiological Response and Symptomatic Clinical Response

Symptomatic Clinical Response	**Per-Patient Microbiological Response**		
	Success	**Failure**	**Indeterminate**
Success	Responder	Non-responder	Indeterminate
Failure	Non-responder	Non-responder	Non-responder
Indeterminate	Indeterminate	Non-responder	Indeterminate

Microbiological response definition due to COVID-19

Due to the COVID-19 pandemic there is a reasonable likelihood that it will not be possible to obtain microbiological samples at the TOC and LFU visits from all patients. The missing samples would not be related to study treatment or procedures, but due to the inability to collect samples during the pandemic. The common practice in cUTI studies of considering indeterminate microbiological response as a non-responder (see above) would not be appropriate in this case and would also have the effect of reducing statistical power down to 85% (with 10% missing data) or 80% (with 20% missing data).

As a result, a set of sensitivity analyses will be performed where microbiological response at TOC and LFU will be defined using a presumed microbiological response if the microbiological data are missing (i.e. Indeterminate) at TOC or LFU as outlined in Table 3. This means that if microbiological data are missing (i.e. Indeterminate) at TOC or LFU respectively, but the symptomatic clinical response is a success, then a patient would be assigned “presumed eradication”; in situations when the symptomatic clinical response is failure a patient would be assigned “presumed persistence”.

Table 3 Definition of Overall response for Per-Patient Microbiological Response and Symptomatic Clinical Response When Using Presumed Microbiological Response

Symptomatic Clinical Response	Per-Patient Microbiological Response		
	Success	**Failure**	**Indeterminate**
Success	Responder	Non-responder	Responder[a]
Failure	Non-responder	Non-responder	Non-responder[b]
Indeterminate	Indeterminate	Non-responder	Indeterminate

[a] based upon presumed eradication; [b] based upon presumed persistence.

5.2 Secondary Endpoints

Clinical and Microbiological Efficacy:

- The proportion of patients with both microbiological success and symptomatic clinical success at TOC in the extended microITT and microbiologically evaluable (ME)-TOC analysis populations.

- The proportion of patients with both microbiological success and symptomatic clinical success at EOT in the microITT, and ME-EOT analysis populations, and at LFU in the microITT, and ME-LFU analysis populations.

- The proportion of patients with per-patient microbiological success at EOT, TOC and LFU in the microITT and relevant ME-EOT, ME-TOC and ME-LFU analysis populations.

- The proportion of patients with symptomatic clinical success at EOT, TOC, and LFU in the microITT, and relevant CE-EOT, CE-TOC and CE-LFU analysis populations.

- The proportion of patients with clinical success based on investigator opinion at TOC in the microITT analysis population.

- The proportion of patients with per-pathogen microbiological success (eradication) at EOT in the microITT and ME-EOT populations, TOC in the microITTand ME-TOC populations, and at LFU in the microITTand 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 microITT and ME-EOT analysis populations, TOC in the microITT and ME-TOC analysis populations, and at LFU in the microITT, and ME-LFU analysis populations.

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

- The proportion of patients with per-pathogen microbiological eradication among those with cefepime-resistant pathogens at EOT in the microITTand ME-EOT populations, TOC in microITT and ME-TOC populations, and at LFU in the microITTand ME-LFU populations.

- The proportion of patients with symptomatic clinical success among those with cefepime-resistant pathogens at EOT in the microITT and CE-EOT populations, TOC in the microITTand CE-TOC populations, and at LFU in the microITT 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 analysis population for patients who have fever (>38°C) at baseline will be assessed as an exploratory endpoint.

In addition to the endpoints listed above, proportion of patients with both microbiological and symptomatic clinical success at TOC, the proportion of patients with symptomatic success at TOC, and per-patient and per-pathogen microbiological success at TOC in the microITT analysis population will be presented by treatment group amongst the subset of patients with MDR pathogens, amongst the subset of patients with ESBL pathogens, by baseline pathogen and also by MIC of baseline pathogen and by disk size. Details of the presentations to be produced are described in Section 7.5.3.

5.2.1 Assessment of Symptomatic Clinical Response

The symptomatic clinical success at TOC in the microITT analysis population is one of the components of the primary endpoint 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), and these data will be used to define pre-morbid symptoms. 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 the protocol.

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.

In the event that all pre-morbid symptoms as measured by the PPSQ take the same values as those measured at baseline on the DPSQ, it will be necessary for all symptoms to be resolved for this patient to be considered a symptomatic clinical success. Similarly, on the rare occasion where an individual symptom as measured by the PPSQ appears to be worse than that measure at baseline on the DPSQ, that symptom would need to subsequently show complete resolution to be considered a success.

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 *For patients with identical symptoms for the pre-morbid PPSQ assessment and baseline DPSQ assessment, all symptoms have to be resolved to be considered a success; If an individual symptom is better at baseline DPSQ when compared with PPSQ, that symptom must subsequently be completely resolved to be considered a success*
Symptomatic clinical failure[a]	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 for the following reasons: • Lost to follow-up • Patient withdrew consent • Missed Visit • One or more symptoms not obtained at relevant visit

cUTI=complicated urinary tract infection; EOT=End of Treatment;
[a] any patient receiving additional antibiotics for the treatment of cUTI after the last dose of randomized therapy but before the EOT visit will be classified a failure

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 *For patients with identical symptoms for the pre-morbid PPSQ assessment and baseline DPSQ assessment, all symptoms have to be resolved to be considered a success. If an individual symptom is better at baseline DPSQ when compared with PPSQ, that symptom must subsequently be completely resolved to be considered a success*
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

For the analysis of clinical endpoints in the microITT and extended microITT analysis populations, the success rate will be calculated as follows:

$$\frac{\text{Number of patients who are a success}}{\text{(Number of patients who are a success + Number of patients who are a failure + Number of patients who have an indeterminate response)}}$$

Patients with an indeterminate response at the EOT, TOC and LFU visits will be excluded from the analysis of clinical response endpoints in the CE and ME analysis populations. For the analysis of clinical response rate in the CE and ME analysis populations, the success rate will be calculated as follows:

$$\frac{\text{Number of patients who are a success}}{\text{(Number of patients who are a success + Number of patients who are a failure)}}$$

In addition to assessing response as success or failure at LFU, responses will be assessed as sustained symptomatic clinical success or symptomatic clinical relapse depending upon the response seen at TOC. Clinical relapse is a sub-category of failure at LFU and includes

patients with clinical success at TOC who are failures at LFU. Patients with clinical success at LFU that are not classified as sustained success at LFU would have been indeterminate at TOC.

5.2.2 General Microbiological Considerations

A baseline urine pathogen is defined as the presence of causative bacteria present at ≥ 105 CFU/mL in baseline urine culture with no more than 2 organisms isolated from the sample collected. A post baseline urine pathogen is defined as the presence of causative bacteria present at ≥ 10^3 CFU/mL in a post baseline urine culture with no more than 2 organisms isolated from the sample collected.

A baseline blood pathogen is defined as a non-contaminant bacteria identified in blood culture obtained at baseline. A post baseline blood pathogen is defined as a non-contaminant bacteria identified in post baseline blood cultures. A patient with a blood pathogen will be considered bacteremic.

Susceptibility to carbapenems including meropenem will be defined using current CLSI criteria[1]. Susceptibility to cefepime/VNRX-5133 will be defined using provisional Susceptible breakpoints of an MIC of ≤16 µg/mL for Enterobacteriaceae, and an MIC of ≤16 µg/mL for *Pseudomonas aeruginosa*. In this case, a provisional Resistant breakpoint would be defined as ≥32 µg/mL.

In addition, a presentation including a provisional Intermediate breakpoint of an MIC of 32 µg/mL will be produced for one or both of the Enterobacteriaceae and *Pseudomonas aeruginosa* organism groups. In this case the categories used will be Susceptible (≤16 µg/mL), Intermediate (32 µg/mL) and Resistant (≥64 µg/mL).

Susceptibility to cefepime (without VRNX-5133) will be defined using current CLSI criteria[1].

The ECMRT will be convened to review all patients prior to database lock and unblinding for inclusion in the clinically and microbiologically evaluable analysis population and to confirm that all baseline pathogens, follow up pathogens, emergent infections and microbiologic outcomes have been appropriately categorized programmatically. For more details on the responsibilities of the ECMRT, refer to the evaluability and clinical/microbiological assessment plan (ECMAP). The source raw data used for evaluability review will be included in SDTM datasets used to generate evaluability review outputs, whilst decisions from the ECMRT review will be included in ADaM datasets.

5.2.3 Assessment of Microbiological Response

The identification of baseline pathogens and the assessment of microbiological response will always use the central laboratory results unless the central laboratory did not receive an isolate. For example, this could be if a sample was not sent, if a sample was lost or if the sample was non-viable. If it is not possible to use central microbiological laboratory results, local microbiological laboratory results will be used.

The definition of per-patient microbiological response will not consider gram-positive pathogens. Per-pathogen microbiological eradication will not be summarized for gram-positive pathogens but will be listed.

The per-patient microbiological response at the TOC visit in the microITT analysis population is one of the components of the primary endpoint. The proportion of patients with both microbiological success and symptomatic clinical success at TOC in the extended microITT, and ME-TOC analysis populations, the per-pathogen microbiological response in the microITT and ME analysis populations at the EOT, TOC, and LFU visits as well as the per-patient microbiological response in the microITT analysis population at EOT and LFU and in the ME analysis 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 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 post-treatment 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 Per-Pathogen Microbiological Response Criteria

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

CFU=colony forming unit.

Persistence will be carried forward such that when persistence is identified, the pathogen will be considered persistent at all subsequent timepoints. In analyses using a presumed persistence definition, presumed persistence will not be carried forward.

As in some cases the response observed at an earlier visit can define the later response, Table 7 summarizes how responses at earlier time points may define subsequent responses.

Table 7: Microbiological response definitions at EOT, TOC and LFU

EOT response	TOC response	LFU response	Additional Comment
Eradication	Eradication	Eradication, Indeterminate or Persistence	Sustained Eradication if LFU response = eradication Recurrence if LFU response = persistence
Eradication	Indeterminate	Eradication, Persistence or indeterminate	
Eradication	Persistence	Persistence (carried forward)	
Indeterminate	Eradication	Eradication, Indeterminate or Persistence	Sustained Eradication if LFU response = eradication

			Recurrence if LFU response = persistence
Indeterminate	Indeterminate	Eradication, indeterminate or persistence	
Indeterminate	Persistence	Persistence (carried forward)	
Persistence	Persistence (carried forward)	Persistence (carried forward)	

For the sensitivity analysis using presumed eradication or presumed persistence, the approach regarding how an earlier visit can define the later response is presented in Appendix 2.

For patients from whom two gram-negative baseline pathogens are isolated, the overall per-patient microbiological response assessment will be a success only if the microbiological response assessment for each of the baseline pathogens is eradication, as outlined in

Table 8.

For patients with both a gram-negative and a gram-positive baseline pathogen, the microbiological response will be based on the response of the gram-negative pathogen only.

Table 8 Definition of Per-Patient Microbiological Response when two gram-negative baseline pathogens are present

Microbiological response of gram-negative Baseline Pathogen #1	Microbiological response of gram-negative Baseline Pathogen #2	Overall per-patient microbiological response
Eradication	Eradication	Success
Eradication	Persistence	Failure
Persistence	Eradication or Persistence	Failure

For circumstances when a pathogen is identified in both blood and urine, the following approach will be taken to defining per-patient microbiological response.

Table 9 Definition of Microbiological Response when blood and urine pathogens are identified

Baseline		Post baseline		Overall per-patient microbiological response
Urine gram-negative pathogen	Blood pathogen	Urine gram-negative pathogen	Blood pathogen	
X	X	X = Eradicated	X = Eradicated	Success
X	X	X = Eradicated	X	Failure
X	X	X = Eradicated	Not done	Success if symptomatic clinical success or failure if symptomatic clinical failure
X	Y	X = Eradicated	Y	Success[a]
X	X, Y	X = Eradicated	X=eradicated, Y	Success[a]
X	None	X= Eradicated	X	Failure

X=pathogen X; Y=pathogen Y. Therefore, these would represent different pathogens

[a] When a different pathogen is isolated in urine and in blood, the blood infection is not considered related to the cUTI. These cases will be described in the CSR.

A pathogen will be said to have microbiologic recurrence at the LFU visit if the response was eradication at the TOC visit and persistence at the LFU visit. Similarly, a pathogen will be said to have sustained eradication at the LFU visit if the response was eradication at the TOC visit and is eradication at the LFU visit. Per-patient microbiologic recurrence is a sub-category of persistence at LFU and will be summarized as a sub-category of failure at LFU. The other subcategory of persistence at LFU include failures that were carried forward from TOC. Sustained eradication is a sub-category of eradication at LFU. Patients with eradication at LFU that are not classified as sustained eradication at LFU would have been indeterminate at TOC.

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

For the analysis of per-patient microbiological endpoints in the microITT and extended microITT analysis populations, the success rate will be calculated as follows:

$$\frac{\text{Number of patients who are a success}}{(\text{Number of patients who are a success} + \text{Number of patients who are a failure} + \text{Number of patients who have an indeterminate response})}$$

Patients with an indeterminate response at the EOT, TOC and LFU visits will be excluded from the analysis of microbiological response endpoints in the CE and ME analysis populations. For the analysis of microbiological response rate in the CE and ME analysis populations, the success rate will be calculated as follows:

$$\frac{\text{Number of patients who are a success}}{(\text{Number of patients who are a success} + \text{Number of patients who are a failure})}$$

5.2.4 Other Microbiological Outcomes

5.2.4.1 By pathogen microbiological response

The by-pathogen microbiological success rate at EOT, TOC and LFU in the microITT analysis population will be calculated as follows:

$$\frac{\text{Number of patients who are a success for the specific pathogen}}{\text{(Number of patients who are a success for the specific pathogen + Number of patients who are a failure for the specific pathogen + Number of patients with an indeterminate outcome for the specific pathogen)}}$$

For each pathogen, the denominator should therefore be equal to the number of patients with a given pathogen identified at baseline.

Patients with an indeterminate Microbiological Response at the EOT, TOC and LFU visits will be excluded from the relevant ME analysis population (ME-EOT, ME-TOC or ME-LFU). Therefore, the by–pathogen Microbiological Response of success will be calculated as follows:

$$\frac{\text{Number of patients with a success for the specific pathogen}}{\text{(Number of patients with a success for the specific pathogen + Number of patients with a failure for the specific pathogen)}}$$

5.2.4.2 Emergent Infections

Pathogens first appearing after baseline in patients with a different baseline pathogen are categorized as described in Table 10 and will be considered separately from microbiological response.

Table 10 Emergent Infection Criteria

Emergent Infection	Definition
Superinfection	Isolation of a new pathogen(s) ≥10^5 (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) ≥10^5 (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

5.2.4.3 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 post-baseline 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.

5.2.5 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 TOC, visit according to the definitions listed in Table 11.

Table 11 Investigator Opinion of Clinical Response Criteria at TOC

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[0] 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[a] are required; however, treatment of asymptomatic bacteriuria is warranted based on the opinion of the investigator
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
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.
[a] This does not include antibacterials that are permitted per protocol for patients with *Enterococcus* or methicillin-resistant *S aureus* infections.

5.3 Exploratory Endpoints

Time to first defervescence (≤37.8°C) in the microITT analysis population for patients who have fever (>38°C) at baseline (based upon vital signs assessments and), where defervescence (≤37.8ºC) is defined as the absence of fever based on the highest temperature recorded on each study day.

Additional presentations will be produced but were not stated in the protocol. These presentations relate to the number of hospital days and time to resolution of all symptoms (in days) based upon PPSQ and DPSQ as outlined in Section 5.2.1. All hospital re-admissions will also be listed.

5.4 Safety Outcomes

Safety will be assessed by analysis of deaths, withdrawals, the occurrence of adverse events (AEs), as well as by adverse changes in laboratory evaluations (chemistry and hematology) and vital signs. 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) [2].

6.0 STATISTICAL METHODS

6.1 Sample Size

The study will randomize at least 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 cUTI) 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%. The anticipated response rate and evaluability rates are estimated based upon recently conducted trials of cUTI. The non-inferiority margin of 15% is justified based upon the FDA Guidance *"cUTI Infections: Developing Drugs for Treatment, June 2018, Revision 1"* [3]. This guidance demonstrates that the benefit of active antibacterial therapy over no treatment (M1) is estimated to be 30% after discounting. Therefore, an NI margin of 15% is considered appropriate.

As the number of patients included in the microITT population is necessary to assure the stated level of power, at least 582 patients will be enrolled to ensure that at least 396 patients will be included in the microITT population.

6.2 Study Visits

Baseline is defined as the last assessment prior to receipt of randomized therapy. Post-baseline is defined as during or after the first dose of study drug.

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 following visit windows are permitted when presenting data at specific visits:

- For efficacy: The nominal visit for EOT, TOC or LFU is to be taken. If the EOT visit occurs before the final dose, but on the same calendar day, this would be deemed a protocol deviation but would not be considered significant to require exclusion for the CE or ME analysis populations.

- For safety: The time window is ±1 calendar day. For example, if the Day 4 laboratory assessments do not occur on Day 4 but laboratory assessments are performed on Day 3 or Day 5 these would be summarized under the Day 4 visit.

6.3 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. The calendar day on which the first dose of study drug is administered 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 cUTI) 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.

6.4 Interim Analysis

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

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.

6.5 Reporting Conventions

- All clinical data will be listed. All listings will include trial, and patient ID.
- Continuous variables will be summarized using number (N), mean, standard deviation (SD), median, minimum, and maximum, while categical data will be presented using frequency counts and percentages.
- For AEs with onset on or after the date of the first dose of study drug, onset day will be calculated as the date of onset of the AE minus the date of the first dose of study drug plus one day. For AEs with onset prior to the date of the first dose of study drug, onset day will be calculated as the date of onset of the AE minus the date of the first dose of study drug. Events with an onset on study day 1 will be assumed to be treatment emergent.
- Prior medications are those taken by the patient prior to randomization. . Concomitant medications are those taken by the patient after randomization. Concomitant medications are those with a start date on or after randomization, or those with a start

date before randomization and a stop date on or after randomization, or with a start date before randomization and are reported as ongoing. When time of medication is not collected (eg, non-antibiotic medications), medications that starts or ends on study day 1 will be considered both prior and concomitant medications.

- For prior medications, start day will be calculated as the start date of the medication minus the date of randomization. For concomitant medications and prior medications taken on the same day as randomization, start day will be calculated as the start date of the medication minus the date of randomization plus one day.

6.6 Handling of Missing Data

Missing data will be handled as follows:

- All missing and partial dates for events occurring after randomization or for medications received after randomization will be queried for a value. If no value can be obtained, substitutions will be made as follows:
  - For start dates, missing year will be defined as the year of the first dose of IV study drug; missing months and days will be defined as "01", as long as this occurs on or after the first dose of study drug. If the algorithm produces a date prior to the first dose of study drug, the date of the first dose of study drug will be used for the partial date.
  - For missing stop dates, medications or advese events will be assumed ongoing.
- The severity and causality assessment for adverse events should not be missing for treatment emergent adverse events and will be queried for a value. Should there be missing data, adverse events with missing severity will be considered severe and adverse events with missing causality will be considered related to study drug provided the event started on or after the first dose of study treatment.
- For clinical and microbiological response, missing data will be handled as follows:
  - Programmatic determination of clinical response: If data for any component of clinical response are missing (PPSQ or DPSQ) such that it cannot be determined if the patient is a clinical success or failure, the patient will be defined as an indeterminate response.
  - Microbiological response: If no interpretable post-baseline specimen is available for a specific visit, the microbiological response for that visit is considered indeterminate.
  - Clinical response based upon Investigator opinion: Patients will be defined an indeterminate response if the Investigator cannot determine if the patient is a clinical cure or failure, if the Investigator did not complete the assessment or if the patient did not complete all relevant assessments provided that the patient was not previously a failure.
- For baseline eGFR and serum creatinine, if the baseline central laboratory data are missing, local laboratory results will be used.
- Local laboratory results will be used if the central laboratory data are missing and the site has received approval from the Sponsor to use baseline or follow up local laboratory data in place of central laboratory data (eg, due to temporary or permanent issues with import/export licenses).

- Missing values for other individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentation.
- When individual data points are missing, categorical data will be summarized including a category for missing.

7.0 STATISTICAL ANALYSES

7.1 Patient Disposition and Protocol Deviations

The number of patients randomized overall, by region, and country will be summarized by treatment group in the ITT analysis population. Region, country and center will be listed.

The number of patients included in each of the study analysis populations (ITT, microITT, Extended microITT, Safety, CE-EOT, CE-TOC, CE-LFU, ME-EOT, ME-TOC and ME-LFU, Safety) will be summarized by treatment group and geographic region. Regions are defined as North America (USA) and Western Europe versus Eastern Europe (Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Romania, Russia, Serbia, Turkey and Ukraine) versus Rest of the World (Argentina, Brazil, China, Mexico and Peru).

The reasons for exclusion from the microITT, Extended microITT, CE-EOT, CE-TOC, CE-LFU, ME-EOT, ME-TOC and ME-LFU and Safety analysis populations will be tabulated. A by-patient listing will be provided that will include the reason(s) for exclusion from each of the study analysis populations.

The number of patients completing the study (ie, completed the LFU visit), prematurely withdrawing from the study, completing study drug, prematurely discontinuing study drug, and the reasons for premature withdrawal and premature discontinuation will be summarized by treatment group and overall for all patients in the ITT analysis population. A listing of study completion/premature withdrawal and study drug completion/premature discontinuation for all patients will be provided.

Premature discontinuation is defined as any patient who stopped study drug prior to their last scheduled dose of treatment on Day 7 or who did not complete study drug treatment according to the investigator.

An important protocol deviation is defined as "*a deviation 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"*. For the purposes of exclusion from the CE and ME analysis populations an important protocol deviation also needs to be considered likely to have an impact on the assessment of clinical efficacy. The review and definition of deviations leading to exclusion from the CE/ME analysis populations will be documented as part of the review by the ECMRT prior to study unblinding.

The number and percentage of patients in the ITT analysis population with at least one important protocol deviation (irrespective of whether this led to exclusion from the CE/ME populations) will be summarized by treatment group and overall. In addition, the number and percentage of patients with at least one important protocol deviation leading to exclusion from the CE/ME analysis populations will be listed. A by-patient listing of all important protocol deviations will also be provided and include a flag for whether the patient was included in the CE/ME analysis populations (Y/N).

7.2 Demographics, Baseline Characteristics and Medical History

Demographic information including sex, ethnicity, race, geographic region of randomization, country of enrollment, age and age category (<65, 65-75 and >75 years), BMI (<18.5, 18.5-24.9, 25-29.9 and ≥30 kg/m^2) and renal status of Normal (GFR ≥ 90 mL/min), Mild impairment (GFR 60-89 mL/min), Moderate (GFR 30-59 mL/min) and Severe (GFR <30 mL/min) will be summarized by treatment group and overall for the ITT and microITT analysis populations.

The number and percentage of patients with each infection type used for randomization stratification (AP only versus cUTI with or without AP) will be summarized for the ITT and microITT analysis populations. Infection type based on actual diagnosis as determined by using symptomatic and other data reported in the eCRF will also be summarized.

The number of patients with bacteremia (Y/N), diabetes (Y/N), prior cUTI within the past year (Y/N), use of antibiotics to treat the current cUTI in the 72 hours prior to the start of study treatment (Y/N), and the number of patients meeting SIRS criteria will be summarized for the ITT and microITT analysis populations. SIRS criteria will be defined as at least two of the following criteria: fever >38.0°C or hypothermia <36.0°C, tachycardia >90 beats/minute, tachypnea >20 breaths/minute, leukocytosis >12*10^9/l or leucopoenia <4*10^9/l. Complicating factor and type of complicating factor will be summarized overall and by type of infection. A by patient listing will also be created.

A summary of the baseline PPSQ, the baseline DPSQ and the symptoms of nausea, vomiting, rigors and chills as well as supra-pubic tenderness and costovertebral angle tenderness on exam will be produced for the ITT and microITT analysis populations and listed. Baseline vital signs will be summarized for the Safety analysis population.

Medical history will be coded into standardized System Organ Classes (SOC), Preferred Terms (PT), and Lower Level Term (LLT) using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1 or later).

Medical history (including diseases/conditions and surgical procedures) will be summarized by treatment group and overall for patients in the ITT and microITT analysis populations. For the summary of medical history, patients with more than one abnormality within the same preferred term will be counted only once for that preferred term.

Demography, baseline characteristics and medical history data will be listed for all patients in the ITT analysis population.

7.3 Baseline Pathogens

A baseline urine pathogen is defined as the presence of causative bacteria present at ≥ 10^5 CFU/mL in baseline urine culture with no more than 2 organisms isolated from the sample collected. Carbapenem resistance is defined in Appendix 1.

The number and percentage of patients with each baseline pathogen will be summarized for the microITT, Extended microITT and ME-TOC analysis populations. This summary will be produced for all patients within each analysis population, by infection type at stratification (AP only versus cUTI with or without AP) and by Enterobacteriaceae baseline gram-negative pathogens (Y/N), ESBL-producing baseline gram-negative pathogens (Y/N), MDR baseline

gram-negative pathogens (Y/N), cefepime-resistant gram-negative pathogens (Y/N) and carbapenem-resistant baseline pathogens (Y/N).

The number and percentage of patients with bacteremia at baseline will be summarized and the number of patients with each different baseline blood pathogen will also be summarized in the microITT and ME-TOC analysis population.

The number and percentage of patients with monomicrobial and polymicrobial (overall and 2 Gram-negative pathogens vs. one Gram-negative and one Gram-positive) infections and with cefepime-resistant pathogens at baseline will be summarized in the microITT analysis population.

For each baseline urine pathogen, a summary of the distribution of minimum inhibitory concentration (MIC) results to each study drug and to cefepime alone will be presented by treatment group and for all patients combined for the microITT, and ME-TOC analysis populations. A similar summary MIC results to each study drug will be produced for blood pathogens in the microITT analysis population (for cefepime/VNRX-5133 MIC and meropenem). Similarly, a summary of the disk zone size distribution to each study drug and to cefepime alone will be produced for urine pathogens in the microITT, and ME-TOC analysis populations and for blood pathogens in the microITT population (for cefepime/VNRX-5133 MIC and meropenem).

A separate susceptibility summary will be produced for cefepime/VNRX-5133 MIC and meropenem in the microITT and ME-TOC populations. The MIC_{50}, MIC_{90}, and MIC range to the specific drug, as well as a tabulated MIC distribution (n at MIC, % at MIC, and cumulative % at MIC) and %S, %I and %R (using CLSI, EUCAST and provisional breakpoints), will be provided. In situations when a patient has both a blood and urine pathogen of a given species, the isolate with the highest MIC to study drug received will be selected for summarization.

A susceptibility summary will also be produced presenting information regarding MIC_{50}, MIC_{90}, MIC range and %S, %I and %R (using CLSI, EUCAST and provisional breakpoints) for all tested antibacterial agents (such as CAZ-AVI) in the microITT and ME-TOC analysis populations.

By-patient listings of pathogen MICs and susceptibilities as determined by the central lab (when available) and interpretations to all drugs tested based on CLSI and EUCAST criteria will also be provided for all patients in the ITT analysis population.

MIC of both study drugs obtained via broth microdilution versus gradient test strip will be plotted for Enterobacteriaceae overall and all baseline gram-negative pathogens seen in ≥ 10 patients in both the microITT and ITT analysis populations. In addition, disk zone size versus MIC result by broth microdilution of both study drugs will be plotted for Enterobacteriaceae overall and all baseline gram-negative pathogens seen in ≥ 10 patients in the microITT and emicroITT analysis populations.

7.4 Extent of Exposure and Study Drug Treatment Compliance

7.4.1 Duration of Study Drug Therapy

Duration of study drug treatment will be summarized for the Safety and microITT Analysis Populations. These summaries will be produced for all patients, and separately for patients

with bacteremia and without bacteremia. Duration of study drug treatment will be calculated as follows: (date of last dose – date of first dose) +1.

The number and percentage of patients who received study drug for 1-2 days, 3-5, 6-8 and >8 for patients without bacteremia and 1-2, 3-5, 6-8, 9-11, 12-14 and >14 for patients with bacteremia will be summarized. Descriptive statistics of the number of days on study drug (n, mean, standard deviation, minimum, median, and maximum) will also be presented by treatment group. Summaries will be provided for all patients, and separately for those patients with and without bacteremia.

Data on duration of study drug therapy will be listed for all patients, along with whether the patient had bacteremia.

Compliance (%) is defined as 100 x (actual number of doses / expected number of doses). The expected number of doses would be calculating based upon the day/time of the patient's last dose and calculating the number of doses expected for that time period. The expected number of doses is based on frequency of dosing as determined at baseline as well as when/if the "impact" field within the estimated Glomerular Filtration Rate (eGFR) CRF is completed as "change in dose". In this case the expected dose will be adjusted accordingly.

Compliance data will be summarized by treatment group for the microITT and Safety analysis populations.

7.4.2 Prior and Concomitant Medications

Prior and/ or concomitant medications will be coded using WHODRUG (Enhanced version Sep 2018, B3 or later).

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 antibacterial therapy, 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.

A summary of receipt of any antibacterial within 72-hours prior to the start of study treatment will be provided by treatment group and overall for the ITT, microITT and CE-TOC Analysis populations. This will include a summary of the reasons for receipt of prior antibacterial therapy (given for cUTI versus given for other indications), a summary of longer versus shorter duration (>24 hours versus ≤24 hours) of prior antibacterial therapy and the type of antibiotic given, summarized by preferred term.

Prior and concomitant non-antibacterial medications will be presented in a listing.

The reasons for receipt of concomitant systemic antibacterial medications will be listed for all patients and summarized by treatment group and for all patients for the ITT, microITT and CE-TOC analysis populations. For concomitant systemic antibacterial medications, the number and percentage of patients will be summarized by antibacterial received, and by

whether the patient was excluded from the CE analysis populations due to receipt of an antibacterial (Yes/No) in the ITT, microITT and CE-TOC analysis populations.

7.5 Efficacy Analyses

For all efficacy analyses, patients will be analyzed in the group to which they were randomized. Unless otherwise stated, patients who are randomized to the wrong randomization strata will be analyzed in the stratum to which they were randomized.

7.5.1 Primary Efficacy Analysis

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

Each patient will be programmatically categorized as a responder, non-responder, or indeterminate based on data on the eCRF. Patients with missing data or who are lost to follow up will be defined as indeterminate for the primary analysis and are included in the denominator for the calculation of the response rate. Thus, patients with an indeterminate response are considered non-responders for the primary analysis. The number and percentage of patients in each treatment group in each response category (success, failure and indeterminate) will be reported.

The null and alternative hypotheses for the primary analysis are:

H_0: P_1-$P_2 \leq -\Delta$
H_1: P_1-$P_2 > -\Delta$
Where P_1 = the primary efficacy outcome rate in the VNRX-5133 group
P_2 = the primary efficacy outcome rate in the meropenem group
Δ = the non-inferiority margin

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.

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 non-inferiority is concluded, a test for superiority will be conducted. In this case, superiority will be concluded if the lower limit of the 95% CI for the difference in response is greater than or equal to zero.

7.5.2 Additional Analyses of the Primary Efficacy Endpoint

A sensitivity analyses stratified by the pre-specified stratification factors of type of infection (AP only versus cUTI) and region (North America and Western Europe versus Eastern Europe versus Rest of the World) will also be performed for the primary endpoint (the proportion of cUTI patients with microbiological and symptomatic clinical success at TOC in the microITT analysis population).

A sensitivity analysis of the primary endpoint at TOC in the microITT population will be performed where the receipt of additional antibacterial therapy given for cUTI will not be considered as a reason for symptomatic clinical failure.

Due to the difficulties in collecting urine samples at TOC due to COVID-19, a sensitivity analysis setting indeterminate microbiological responses to presumed eradication or presumed persistent based upon clinical response will be performed, as described in Section 5.1.

An additional sensitivity analysis will be performed for the primary outcome at TOC in the ME-TOC population, but excluding patients who had an indeterminate clinical outcome at the TOC visit (i.e. includes patients who are in **both** the ME and CE populations).

For all sensitivity analyses, a 95% confidence interval using the method proposed with stratification by Miettinen and Nurminen will be computed for the difference in primary endpoint between VNRX-5133 minus meropenem. Cochran-Mantel-Haenzsel weights will be used for the stratum weights in the calculation of the CI.

Subgroup analyses of the primary efficacy outcome and for microbiological response at TOC and symptomatic clinical response at TOC in the microITT analysis population will also be conducted for descriptive purposes. Forest plot of the treatment difference and 95% CI will be produced for the following subgroups:

- Age category (<65, 65-75, >75 years)
- Race
- Sex
- Region (North American & Western Europe versus Eastern Europe versus Rest of World)
- Diagnosis for the purposes of stratification (AP only versus cUTI with or without AP)
- Prior antibiotics (Y/N) (in the previous 72 hours)
- Baseline renal status (normal (GFR > 90 mL/min) versus mild impairment (GFR 60-89 mL/min) versus moderate impairment (GFR 30-59 mL/min)
- Bacteremia (Y/N)
- Complicating factor present (Y/N) and type of Complicating Factor
- SIRS (as defined in Section 7.2).
- Diabetes (Y/N)
- Prior cUTI in last year (Y/N)
- Monomicrobial v polymicrobial infections [monomicrobial, polymicrobial (2 gram-negative), polymicrobial (1 gram-negative, 1 gram-positive)]

If any of the above subgroups indicate a difference in treatment effect, further evaluation will be undertaken to understand whether such differences apply for patients with AP and those with cUTI.

A Forest plot of the treatment difference in primary endpoint and CI by the stratification factors and subgroups will be provided.

7.5.3 Secondary Efficacy Analyses

The following secondary endpoints will use the same analysis method as the primary endpoint. For summaries of both microbiological and symptomatic clinical response,

microbiological response and symptomatic clinical response all outcomes (success, failure, relapse/recurrence [LFU only], and indeterminate) will be presented for analyses performed at EOT, TOC and LFU in the microITT analysis population. For all other secondary and additional analyses, outcomes of success will be presented unless otherwise specified.

Forest plots will be produced to demonstrate both microbiological and symptomatic clinical success, microbiological success and symptomatic clinical success at EOT, TOC and LFU in the microITT, extended microITT (composite success), relevant ME analysis populations (composite and microbiological success only) and relevant CE analysis populations (symptomatic clinical success only).

No formal non-inferiority margin is defined for the secondary endpoints, but rather the aim is to assess consistency of treatment effect with the primary efficacy analysis. A forest plot will be produced for each of the following endpoints along with a summary of the number and percentage of patients with a success, presented by treatment group and for all patients.

- The proportion of patients with both microbiological and symptomatic clinical success at TOC in the Extended microITT, and ME-TOC analysis populations
- The proportion of patients with both microbiological success and symptomatic clinical success at EOT in the microITT and ME-EOT analysis populations, and at LFU in the microITT and ME-LFU analysis populations
- The proportion of patients with per-patient microbiological success at EOT, TOC and LFU in the microITT, ME-EOT, ME-TOC and ME-LFU analysis populations
- The proportion of patients with symptomatic clinical success at EOT, TOC, and LFU in the microITT, CE-EOT, CE-TOC and CE-LFU analysis populations
- The proportion of patients with clinical success based on investigator opinion at TOC in the microITT analysis population.

The following secondary endpoints are expected to involve a smaller number of patients and/or involve the summary of a large number of individual pathogens. As such, these data will be summarized including all pathogens including ≥10 patients across both treatment groups:

- The proportion of patients with both microbiological success and symptomatic clinical success among those with cefepime-resistant pathogens at EOT in the microITT and ME-EOT analysis populations, TOC in the microITT and ME-TOC analysis populations, and at LFU in the microITT and ME-LFU analysis populations.
- The proportion of patients with per-patient microbiological success at EOT, TOC and LFU among those with cefepime-resistant pathogens in the microITT and ME-EOT, ME-TOC, and ME-LFU analysis populations
- The proportion of patients with symptomatic clinical success at EOT, TOC and LFU among those with cefepime-resistant pathogens in the microITT and CE-EOT, CE-TOC, and CE-LFU analysis populations
- The proportion of patients with per-pathogen microbiological eradication at EOT in the microITT and ME-EOT populations, TOC in the microITT and ME-TOC populations, and LFU in the microITT and ME-LFU populations
- The proportion of patients with per-pathogen microbiological eradication at EOT, TOC and LFU among those with cefepime-resistant pathogens in the microITT and ME-EOT, ME-TOC and ME-LFU analysis populations

In addition, the following data will be summarized:

- Both microbiological and symptomatic clinical success at EOT, TOC and LFU by baseline pathogen in the microITT and ME-EOT, ME-TOC, and ME-LFU analysis populations
- Per-patient microbiological success at EOT, TOC, and LFU by baseline pathogen in the microITT analysis population
- Symptomatic clinical success at EOT, TOC, and LFU by baseline pathogen in the microITT analysis population
- The proportion of patients with both microbiological and symptomatic clinical success at TOC, the proportion of patients with symptomatic success and per-patient and per-pathogen microbiological success at TOC amongst patients with and without Enterobacteriaceae, multidrug resistant (MDR) pathogens and extended spectrum beta-lactamase (ESBL) pathogens in the microITT analysis population. The definition of MDR and ESBL pathogens are included in Appendix 1.

A Forest plot which demonstrates both microbiological and symptomatic clinical success, microbiological success, and symptomatic clinical success at TOC by baseline pathogen and baseline gram-negative sub-groups (cefepime-resistant, Enterobacteriaceae, ESBL producing, MDR) in the microITT analysis population will be produced. This plot will only include baseline pathogens and gram-negative category groups where there are at least 10 patients (total across both treatment groups) with the relevant baseline pathogen.

The following summary tables will only be produced where there are at least 10 patients (total across both treatment groups) with the relevant baseline pathogen.

- The Proportion of patients with both microbiological and symptomatic clinical success at TOC will be summarized by MIC of the baseline pathogen for both study drugs and cefepime alone as well as by disk size for all 3 drugs, in the microITT and ME-TOC analysis populations.
- The proportion of patients with microbiological success at TOC will be summarized by MIC of the baseline pathogen for both study drugs and cefepime alone as well as by disk size for all 3 drugs, in the microITT and ME-TOC analysis populations.
- The proportion of patients with symptomatic clinical response at TOC will be summarized by MIC of the baseline pathogen for both study drugs and cefepime alone as well as, and by disk size for all 3 drugs, in the microITT and ME-TOC analysis populations.

For all by-pathogen analyses, patients with a pathogen of the same genus and species with more than one phenotype will be counted once for the overall tabulation of the pathogen, for example, *E. coli*. In this case, the pathogen with the highest MIC to study drug received will be taken for the purposes of presentation.

A summary of the DPSQ categories (absent/mild/moderate/severe) will also be produced with a shift table of change in category from baseline to each visit in the microITT analysis population.

A listing of baseline pathogen genus and species, MIC to study drug received, symptomatic clinical success, microbiological success and clinical success based on investigator opinion at the EOT, TOC and LFU visits will be produced for all patients in the extended microITT population.

All patients with a superinfection or new infection will also be identified in a listing.

Patients showing at least one pathogen with decreasing susceptibility will be listed, and will include information on pathogen, study day, MIC value by day and susceptibility to study drug received. This is defined as persistence with a ≥4-fold increase in MIC to study drug received versus baseline.

7.5.4 Additional Efficacy Analyses

A sensitivity analysis will be performed in which all patients with a gram-negative uropathogen isolated at study entry at ≥10^4 CFU/mL will be included. This sensitivity analysis will be performed for the endpoints of overall (clinical and microbiological) response at TOC, symptomatic clinical success at TOC, per-patient microbiological success at TOC and per-pathogen microbiological eradication in the microITT and extended microITT populations.

Concordance between microbiological and symptomatic clinical responses at EOT, TOC and LFU will be summarized by treatment group in the microITT analysis population. In addition, the reasons for non-response or indeterminate response for symptomatic clinical success at EOT, TOC and LFU will be summarized in the microITT analysis population.

All post-baseline uropathogens of the same genus and species as the corresponding baseline uropathogen(s) from the same patient will undergo epidemiology typing to assess relatedness (clonality). Data will be used to further characterize persistent infections. The number and percentage of failures at EOT, TOC and LFU with a post-baseline pathogen clonally related to the baseline pathogen will be summarized in the microITT analysis population, as will the number and percentage of failures with a post-baseline pathogen clonally unrelated to the baseline pathogen. Typing results will also be listed. Relatedness of post-baseline pathogens to baseline pathogens from the same patient will be assessed and determined by the Evaluability and Clinical/ Microbiologic Review Team.

All baseline and post-baseline Enterobacteriaceae and *Pseudomonas aeruginosa* clinical isolates that meet the MIC screening criteria outlined in Appendix 1 will undergo genotypic characterization to identify the presence of β-lactam resistance and other resistance mechanisms. Composite clinical and microbiological, symptomatic clinical, and microbiological responses will be summarized based on presence or absence of β-lactamase as well as by specific β-lactamase present. β-lactam resistance mechanisms present in clinical isolates that display development of resistance to cefepime/VNRX-5133 during treatment or MIC result(s) of post-baseline strain(s) ≥4-fold higher when compared with the respective baseline isolate will be described. Results of all genotypic testing for β-lactam resistance and other resistance mechanisms will be listed.

The time to first defervescence (≤37.8°C) will be assessed for patients in the microITT analysis population 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 using a Kaplan-Meier plot. It will also be summarized as the mean, median, minimum, and maximum number of days and number of patients by treatment and by treatment and use of prior antibiotics Y/N.

Time to resolution of all symptoms will be presented for the microITT analysis population using the same method as for time to first defervescence.

Number of hospital days and the number of hospital days since randomization will be summarized for patients in the microITT analysis population by mean, SD, minimum, median, maximum and number of patients. The number and percent of patients with each number of days of hospitalization will also be presented.

Time to defervescence, number of hospital days and the time to resolution of each individual symptom will be listed by patient.

7.6 Safety Analyses

All safety analyses will be conducted in the Safety analysis population. Patients who receive the wrong study drug for their entire course of treatment will be analyzed in the group based on the drug received. Patients who receive the wrong study drug less than the entire course of treatment will be analyzed as predominantly treated and will be highlighted in the listings and included as a footnote to the summary tables.

7.6.1 Adverse Events

Adverse events (AEs), including SAEs, will be collected from the time of informed consent to the last study visit. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 or higher.

A treatment emergent adverse event (TEAE) is defined as an AE that occurs during or after treatment through the last study visit. This is defined as any AE that starts or worsens during that time through the last study visit. If the AE start date is unknown or is a partial date such that it cannot be determined if the AE started on or after the first study drug administration, it will be categorized as a TEAE.

An overall summary of AEs will include the number of patients who experienced at least one AE of the following categories: any AE, any TEAE, any serious TEAE, any drug-related TEAE, any drug-related serious TEAE, any TEAE leading to premature discontinuation of study drug, any TEAE leading to death, any drug-related TEAE leading to premature discontinuation of study drug and any drug-related TEAE leading to death.

The number and percentage of patients reporting TEAEs, 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 decreasing frequency of preferred term (PT).

The number and percentage of patients reporting related TEAEs, TEAEs resulting in discontinuation of study drug, related TEAEs resulting in discontinuation of study drug, SAEs, related SAEs and SAEs resulting in discontinuation of study drug will be summarized by treatment and presented by SOC and decreasing frequency of PT.

The number and percentage of deaths due to AEs and disease progression will be summarized.

If the same AE (based on preferred term) is reported for the same patient more than once, the AE is counted only once for that preferred term at its highest severity and strongest relationship to study drug.

A summary of TEAEs and a summary of SAEs sorted by decreasing frequency of preferred term in cefepime/VNRX-5133 patients will also be provided.

A listing of all TEAES and all TEAEs leading to discontinuation of study drug will be provided and will include date and onset day of the AE, duration, system organ class, preferred term, verbatim term, seriousness, severity, relationship to study drug administration, action taken, and outcome.

A listing of all serious TEAEs will also be provided and will include date and onset day of the serious AE, duration, system organ class, preferred term, verbatim term, severity, relationship to study drug administration, action taken, outcome, and date and onset day of death (where applicable).

A listing of all deaths will include cause of death, date and onset day of death, as well as age, sex, diagnosis, bacteremia Y/N and baseline renal category.

7.6.2 Clinical Laboratory Evaluations

All blood and urine specimens will be sent to a central reference laboratory for analysis and testing.

Clinical laboratory data collected during scheduled visits and analyzed at the central laboratory (i.e., clinical chemistry, hematology, urinalysis, and coagulation parameters) will be summarized by assessment and by timepoint including the actual value and change from baseline; normal, high and low parameters based on each parameter's reference range will be summarized by visit, and compared to baseline (ie, shift tables). All data (scheduled and unscheduled visits and from central and local laboratories) will be listed, and out of range values flagged. eGRF (based on Modification of Diet in Renal Disease [MDRD] formula) will be derived based on central laboratory serum creatinine results and summarized and listed.

Calculation of eGFR by MDRD:

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

where Scr is serum creatinine in mg/dL and eGFR is measured in mL/min/1.73m^2.

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

The number and percent of patients with treatment-emergent potentially clinically significant (PCS) laboratory values (as defined in Table 12) at any time post-baseline and by visit will be tabulated for each treatment group. This assessment will use all scheduled and unscheduled non-missing central laboratory data except in specific instances of missing scheduled central

laboratory data as described in Section 6.6 where local laboratory data will be used. Plots of central laboratory values (or local laboratory values in specific instances described in Section 6.6) by visit for laboratory parameters will also be produced.

Table 12 Criteria for Potentially Clinically Significant Laboratory Results

Parameter	Low value and change from baseline	High value and change from baseline
HEMATOLOGY		
Hemoglobin	<0.8 x LLN and >20% decrease	>1.3 x ULN and >30% increase
Hematocrit	<0.8 x LLN and >20% decrease	>1.3 x ULN and >30% increase
Leukocytes (white blood cells)	<0.65 x LLN and >60% decrease	>1.6 x ULN and >100% increase
Neutrophils	<0.65 x LLN and >75% decrease	>1.6 x ULN and >100% increase
Lymphocytes	<0.65 x LLN and >75% decrease	>1.6 x ULN and >100% increase
Eosinophils	NA	>4 x ULN and >300% increase
Monocytes	NA	>4 x ULN and >300% increase
Basophils	NA	>4 x ULN and >300% increase
Platelets	<0.65 x LLN and >50% decrease	>1.5 x ULN and >100% increase
COAGULATION		
Prothrombin time	NA	>1.5 x ULN and >100% increase
International normalized ratio	NA	>1.5 x ULN and >100% increase
Partial thromboplastin time	NA	>2 x ULN and >100% increase
CHEMISTRY		
Sodium	<0.85 x LLN and >10% decrease	>1.1 x ULN and >10% increase
Potassium	<0.8 x LLN and 20% decrease	>1.2 x ULN and >20% increase
Creatinine	NA	>2.0 x ULN and>100% increase
Blood Urea Nitrogen	NA	> 3.0 x ULN and >200% increase
Calcium	<0.7 x LLN and >30% decrease	>1.3 x ULN and >30% increase
Magnesium	<0.5 x LLN and >50% decrease	NA
Phosphorus	<0.5 x LLN and >50% decrease	>3.0 x ULN and >200% increase
Alkaline phosphatase	<0.5 x LLN and >80% decrease	>2.0 x ULN and >100% increase
Alanine aminotransferase	NA	>3.0 x ULN and >200% increase
Aspartate aminotransferase	NA	>3.0 x ULN and >200% increase
Gamma-glutamyl transferase	NA	>3.0 x ULN and >200% increase
Total bilirubin	NA	>2.0 x ULN and >150% increase
Direct bilirubin	NA	>2. 0 x ULN and >150% increase

The number and percentage of patients in each treatment group with an elevated transaminase level (>3 x ULN, >5 x ULN, and >10 x ULN), an elevated bilirubin level (>1.5 x ULN and >2 x ULN) with and without an elevated alkaline phosphatase (ALP) level [>2.0 x ULN] will be presented by treatment group up to EOT, up to TOC and up to LFU. This assessment will use all scheduled and unscheduled data obtained at both local and central laboratories.

Actual laboratory values and change from baseline values will be listed for all patients within the Safety analysis population.

A listing will be produced for patients who meet the reportable liver abnormalities criteria. These are:

- ALT or AST >3xULN AND Total bilirubin >2xULN
- ALT or AST >10x ULN
- Potential Hy's law, defined as (ALT or AST)>3x ULN, total bilirubin >2x ULN, and alkaline phosphatase <2x ULN. These assessments will be based upon scheduled and unscheduled visits and using data from the central and local laboratories).

7.6.3 Vital Signs and ECG

Vital signs include heart rate, respiratory rate, temperature (oral or tympanic), and blood pressure. Descriptive statistics at each visit, and the change from baseline at each post-baseline visit will be summarized by treatment group. Change from baseline will be calculated for each patient at the specified Visit as the value at the specified Visit minus the baseline value.

Actual vital signs values and change from baseline will be listed for all patients.

No analysis of ECG data is planned.

8.0 CHANGES FROM THE PROTOCOL SPECIFIED ANALYSES

Due to the COVID-19 pandemic there is a reasonable likelihood that microbiological samples at the TOC and LFU will not be available from all patients. Therefore, sensitivity analyses will be performed where microbiological response at TOC and LFU will be defined using presumed microbiological response if the microbiological data are Indeterminate.

The proportion of patients with both microbiological success and symptomatic clinical success (overall response) at EOT, TOC, and LFU will not be assessed for the clinically evaluable population. Microbiological data is necessary to assess overall response and are not always available for patients included in the CE population.

An additional sensitivity analysis has been added which will include patients with a gram-negative uropathogen at study entry ≥10^4 CFU/mL for the endpoints of overall (clinical and microbiological) response, clinical success, per-patient microbiological success and per-pathogen microbiological eradication at TOC in the microITT and extended microITT populations.

9.0 LIST OF MAJOR CHANGES FROM THE ORIGINAL STATISTICAL ANALYSIS PLAN

This is version 6.0 of the statistical analysis plan. The original version, 1.0, was dated 09 March 2020. Version 2.0 was dated 30 March 2021. Version 3.0 was dated 19 April 2021. Version 4.0 was dated 24 September 2021, Version 4.1 was dated 02 November 2021, and Version 5.0 was dated 30 November 2021. Table 13 lists the major changes from the original version of the statistical analysis plan and the rationale for each change. Only minor changes were made to Version 3.0.

Table 13 Major changes from the original version of the Statistical Analyais Plan

SAP Version	Change Description	Sections Impacted	Rationale for Change
6.0	Text referring to the use of presumed response for the primary analysis is removed. Specifically, "In the event ≥10% of microbiological data are missing at TOC, microbiological response at TOC will be defined using presumed response for the primary analysis. In this case a sensitivity analysis will be performed setting missing microbiological data at TOC to indeterminate" was removed.	5.1 Primary Endpoint 7.5.2 Additional Analyses of the Primary Efficacy Endpoint	COVID impact on TOC visits did not meet 10% threshold.
6.0	Table 9 table clarified for bacteremic patients without post-baseline blood cultures. Microbiological response will be defined using a presumed microbiological response based on the symptomatic clinical response.	5.2.3 Assessment of Microbiological Response	U.S. Food and Drug Administration
5.0	The provisional susceptible breakpoint of cefepime/VNRX-5133 was updated from an MIC of ≤8 µg/mL to an MIC of ≤16 µg/mL for both Enterobacteriaceae and *Pseudomonas aeruginosa*.	4.2 Microbiological ITT (microITT) Analysis Population; 5.2.2 General Microbiological Considerations	The extended duration of infusion of cefepime / VNRX-5133 support MICs of ≤16 µg/mL using the optimized administered doses in the cUTI trial.
4.0	The proportion of patients with both microbiological success and symptomatic clinical success at EOT, TOC, and LFU will not be assessed for the clinically evaluable population	5.2 Secondary Endpoints; 7.5.3 Secondary Efficacy Analyses	The microbiological data required to assess overall response are not always available for patients included in the CE population.
4.0	Updated the sample size from "582 patients" to "at least 582 patients."	6.1 Sample Size	Clarify that more than 582 patients may be required to ensure an adequate number of patients in the microITT population.
4.0	A sensitivity analysis will be performed in which all patients with a gram-negative uropathogen isolated at study entry at ≥10^4 CFU/mL will be included. This sensitivity analysis will be performed for the endpoints of overall (clinical and microbiological) response at TOC, symptomatic clinical success at TOC, per-patient microbiological success at TOC and per-pathogen microbiological eradication in the microITT and extended microITT populations.	7.5.4 Additional Efficacy Analyses	Microbiological success is defined as a CFU count < 10^3 CFU/mL. Therefore patients with a uropathogen isolated at study entry at ≥10^4 CFU/mL can be evaluated for a microbiological response.
2.0	Added Microbiological Response Definition due to COVID-19. A set of sensitivity analyses will be performed	5.1 Primary Endpoint	A sensitivity analysis and a potential alternative

	where microbiological response at TOC and LFU will be defined using a presumed microbiological response if the microbiological data are missing (i.e., Indeterminate) at TOC or LFU. In the event ≥10% of microbiological data are missing at TOC, microbiological response at TOC will be defined using presumed response for the primary analysis. In this case a sensitivity analysis will be performed setting missing microbiological data at TOC to indeterminate.		primary endpoint was introduced due to a higher likelihood that the COVID-19 pandemic would result in missing microbiological data and increases in indeterminate responses.
2.0	The assessment of symptomatic clinical response was clarified when there are discrepancies between the DPSQ and PPSQ. In the event that all pre-morbid symptoms as measured by the PPSQ take the same values as those measured at baseline on the DPSQ, it will be necessary for all symptoms to be resolved for this patient to be considered a symptomatic clinical success. Similarly, on the rare occasion where an individual symptom as measured by the PPSQ appears to be worse than that measure at baseline on the DPSQ, that symptom would need to subsequently show complete resolution to be considered a success.	5.2.1 Assessment of Symptomatic Clinical Response	Clarification to response definition.
2.0	The assessment of symptomatic clinical response was clarified that symptomatic clinical failure was not carried forward to subsequent endpoints.	5.2.1 Assessment of Symptomatic Clinical Response	Clarification to response definition.
2.0	The assessment of symptomatic clinical response at EOT was clarified. Any patient receiving additional antibiotics for the treatment of cUTI after the last dose of randomized therapy but before the EOT visit will be classified a failure.	5.2.1 Assessment of Symptomatic Clinical Response, Table 4, footnote [a]	Clarification to response definition.
2.0	CE and ME population definitions were updated to specify that the endpoint definition excludes patients with an indeterminate response or the endpoint was evaluated outside the protocol defined window.	4.4 Clinically Evaluable Analysis Populations; 4.5 Microbiologically Evaluable Populations	Clarification to population definition.

10.0 REFERENCES

1. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 31st ed. CLSI supplement M100. CLSI, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2021.
2. ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline, E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Note for Guidance on Clinical Safety Data Management, June 1995.
3. Guidance for Industry. Complicated Urinary Tract Infections: Developing Drugs for Treatment. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Revision 1, June 2018.
4.

APPENDIX 1
DEFINITIONS OF CARBAPENEM RESISTANCE, MDR AND ESBL PATHOGENS

Carbapenem resistance is defined as the following:

- Enterobacteriaceae: meropenem MIC ≥4 μg/mL
- *P. aeruginosa*: meropenem MIC ≥8 μg/mL and/or imipenem MIC ≥8 μg/mL

Extended-spectrum β-lactamases (ESBLs) are β-lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain (e.g. cefuroxime, cefotaxime, ceftriaxone, ceftazidime and cefepime) and aztreonam, an oxyimino monobactam. For the purpose of the VNRX-5133-201 SAP and based on the limited number of antibacterial agents that are being tested at the central laboratory, ESBL producers would be defined as isolates of Enterobacteriaceae with ceftazidime and/or aztreonam and/or cefepime MIC ≥2 μg/mL. These isolates, as well as isolates of *P. aeruginosa* with ceftazidime MIC ≥16 μg/mL and/or imipenem or meropenem MIC ≥2 μg/mL will be assessed for β-lactamase content and other resistance mechanisms.

Multidrug-resistant (MDR) organisms are those that are non-susceptible to at least one agent in three or more categories of antibacterial agents (Magiorakos et al. 2012. CMI 18:268-281). For the purpose of the VNRX-5133-201 SAP, and based on the limited number of antibacterial agents that are being tested at the central laboratory, MDR organisms would be defined as isolates of Enterobacteriaceae or *P. aeruginosa* that are resistant to at least one agent from three or more categories in the corresponding tables below:

Enterobacteriaceae

Agents to be tested at CCLS	**Category**	**Exceptions due to intrinsic resistance***
Aztreonam	Monobactam	
Cefepime, ceftazidime	Extended-spectrum cephalosporin	
Cefepime/VNRX-5133	Extended-spectrum cephalosporin + boronate β-lactamase inhibitor	
Tobramycin	Aminoglycoside	*P. stuartii*
Ceftazidime/avibactam, ceftolozane/tazobactam	Extended-spectrum cephalosporin + β-lactamase inhibitor	
Imipenem, meropenem	Carbapenem	
Meropenem/vaborbactam	Carbapenem + boronate β-lactamase inhibitor	
Ampicillin/sulbactam	Penicillin + β-lactamase inhibitor	*C. freundii, K. aerogenes, E. cloacae, H. alvei, S. marcescens*
TMP/SMX	Folate pathway inhibitor	
Levofloxacin	Fluoroquinolone	
Piperacillin/tazobactam	Antipseudomonal penicillin + β-lactamase inhibitor	
Tetracycline	Tetracycline	*P. mirabilis, P. penneri, P. vulgaris, P. rettgeri, P. stuartii*

*These organisms are intrinsically resistant to the noted agents (CLSI M100 Appendix B Table B1).

P. aeruginosa*

Agents to be tested at CCLS	**Category**
Aztreonam	Monobactam
Cefepime, ceftazidime	Extended-spectrum cephalosporin
Cefepime/VNRX-5133	Extended-spectrum cephalosporin + boronate β-lactamase inhibitor
Tobramycin	Aminoglycoside
Ceftazidime/avibactam, ceftolozane/tazobactam	Extended-spectrum cephalosporin + β-lactamase inhibitor
Imipenem, meropenem	Carbapenem
Meropenem/vaborbactam	Carbapenem + boronate β-lactamase inhibitor
Levofloxacin	Fluoroquinolone
Piperacillin/tazobactam	Antipseudomonal penicillin + β-lactamase inhibitor

**P. aeruginosa* is intrinsically resistant to ampicillin/sulbactam, TMP/SMX and tetracycline (CLSI M100 Appendix B Table B2) hence those agents are not included in the table.

APPENDIX 2
PER PATHOGEN MICROBIOLOGICAL RESPONSE DEFINITIONS WHEN USING PRESUMED ERADICATION AND PRESEUMED PERSISTENCE

Microbiological Response definitions at EOT, TOC and LFU

EOT response	TOC response	LFU response	Additional Comment
Eradication (Documented or Presumed)	Eradication (Documented or Presumed)	Eradication (Documented or Presumed), Persistence (Documented or Presumed), or Indeterminate,	Sustained Eradication if LFU response = eradication (Documented or Presumed) Recurrence if LFU response = persistence (Documented or Presumed)
Eradication (Documented or Presumed)	Indeterminate[a]	Eradication (Documented or Presumed), Persistence (Documented or Presumed), or Indeterminate,	
Eradication	Persistence	Persistence (carried forward)	
Eradication	Presumed Persistence	Eradication (Documented or Presumed), Persistence (Documented or Presumed) or Indeterminate	
Indeterminate[a]	Eradication (Documented or Presumed)	Eradication (Documented or Presumed), Persistence (Documented or Presumed), or Indeterminate,	Sustained Eradication if LFU response = eradication (Documented or Presumed) Recurrence if LFU response = persistence (Documented or Presumed)
Indeterminate[a]	Indeterminate[a]	Eradication (Documented or Presumed), or persistence (Documented or Presumed), or Indeterminate	
Indeterminate[a]	Persistence	Persistence (carried forward)	
Indeterminate[a]	Presumed Persistence	Eradication (Documented or Presumed), Persistence (Documented or Presumed), or Indeterminate	
Persistence	Persistence (carried forward)	Persistence (carried forward)	
Presumed Persistence	Eradication (Documented or Presumed),, Persistence (Documented or Presumed), or indeterminate	Eradication (Documented or Presumed),, Persistence (Documented or Presumed), or Indeterminate	

[a] Indeterminate response only possible if clinical response is indeterminate and microbiological response is missing

Per-Patient Microbiological Response with two gram-negative baseline pathogens

Microbiological response of gram-negative Baseline Pathogen #1	Microbiological response of gram-negative Baseline Pathogen #2	Overall per-patient microbiological assessment
Eradication or Presumed Eradication	Eradication or Presumed Eradication	Success
Eradication or Presumed Eradication	Persistence or Presumed Persistence	Failure
Persistence or Presumed Persistence	Eradication, Presumed Eradication, Persistence or Presumed Persistence	Failure