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TITLE PAGE

Protocol Title: A Phase 1, Open-label Study to Evaluate the Safety and Plasma and Intrapulmonary Pharmacokinetics of Ceftibuten and Ledaborbactam in Healthy Adult Participants

Protocol Number: VNRX-7145-105-01

Compound: Ceftibuten-ledaborbactam etzadroxil

Brief Title: Plasma and Intrapulmonary Pharmacokinetics of Ceftibuten and Ledaborbactam in Healthy Male and Female Participants 18 to ≤55 Years of Age

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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Identifier Numbers:

IND 133963

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Approval Date: 25-September-2024

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Sponsor Signatory:

Representative(s) of Venatorx Pharmaceuticals, Inc. who agree to the terms and conditions of this protocol:

Signed by: [redacted]
Signing Reason: I approve this document
Signing Time: 01-Oct-24 | 7:15:49 AM PDT

[redacted] 01-Oct-24

Date

Medical Monitor Name and Contact Information will be provided separately

Investigator Signatory:

The signature of the Investigator below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States state and federal regulations, all other applicable local regulatory requirements, in accordance with Good Clinical Practices (GCPs) including International Council for Harmonization (ICH) Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

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

Principal Investigator Printed Name _____

Signature and Date _____

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	19-Mar-2024

Amendment 1 (25-September-2024)

Overall Rationale for the Amendment:

The primary driver for the protocol changes is to implement an additional tolerability assessment, namely stool frequency and characterization.

Section # and Name	Description of Change	Brief Rationale
1.2 Schedule of Activities	Removed "X" from the Screening column in the Adverse Events monitoring row in the SOA	Adverse Events will be monitored from Day -1 to the Follow-up visit, as outlined in the associated footnote. This adjustment ensures that AE monitoring is consistent and comprehensive throughout the study period.
Synopsis and Section 3 Objectives and Endpoints	• Tolerability added to the secondary objective related to safety	To ensure changes in bowel habits are assessed and analyzed as a measure of tolerability
1.2 Schedule of Activities	• Added a row for bowel movement assessment • added bowel movement assessment to medical history footnote "b" • created new footnote "o" to describe bowel movement assessment • original footnote o changed to footnote p	
8.3.7 Bowel Movement Assessment	Created new section in study procedures to describe bowel movement assessment and participant diary	
10.7 Appendix 7	Added Appendix 7 "Bowel Movement Diary"	

Section # and Name	Description of Change	Brief Rationale
5. Study Population, Table 1 Permitted Laboratory Values at Screening and/or Day-1 for Inclusion	ALT/SGPT and AST/SGOT inclusion values changed from ≤ULN to ≤1.5×ULN	This revision allows some flexibility in enrolling participants with borderline non-clinically significant abnormal results for these analytes in alignment with the acceptable total bilirubin levels.
5.3.3 Activity	Revised language to align with the related inclusion criterion 13	This revision clarified the activities that are not allowed during the study.
7.1 Discontinuation of Study Intervention	Moved language related to individual halting criteria to a newly created Section 7.2.1; a cross-reference to this new section was added to Section 10.1.5.	This revision moves the individual halting criteria to a more appropriate section to distinguish it from the language related to study discontinuation.
Section 8 Study Assessments and Procedures	Made administrative changes to Section 8 to align with the Venatorx template	Administrative changes were made to this section to align with the Venatorx template and other Phase 1 protocols.
Section 8.1 Administrative and General Procedures	Created new section 8.1 with template language from the Venatorx template	
Section 8.1.1 Medical History/ Demography	Created new section 8.1.1 to describe collection of medical history data	
Section 8.5.1	Reference to discarding the cell pellet has been removed	Detailed instructions will be included in the Lab Manual
Section 8.5.2 Blood Sample Collection for Drug and Urea Assay	Added storage conditions for plasma samples collected for pharmacokinetic analyses	Storage conditions were added to ensure sufficient details are included in the protocol.
Section 10.1.3 Informed Consent Process	Added language to address the informed consent process for a partner pregnancy	Administrative changes were made to this section to align with the Venatorx template and other Phase 1 protocols.
10.3.4 Reporting of SAEs	Changed method of SAE reporting to “Email”	The heading of this section was incorrect, as Email is the method used to report SAEs, not a paper source.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, Open-label Study to Evaluate the Safety and Plasma and Intrapulmonary Pharmacokinetics of Ceftibuten and Ledaborbactam in Healthy Adult Participants

Brief Title: Safety and Plasma and Intrapulmonary Pharmacokinetics of Ceftibuten and Ledaborbactam in Healthy Male and Female Participants 18 to ≤55 Years of Age

Rationale:

This study is being conducted to compare the intrapulmonary pharmacokinetics (PK) to the plasma PK of ceftibuten and ledaborbactam to inform dose selection for a future Phase 3 study evaluating the efficacy of ceftibuten-ledaborbactam etzadroxil for the treatment of lower respiratory tract infections.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the steady-state intrapulmonary PK and plasma PK of ledaborbactam and ceftibuten following administration of ceftibuten-ledaborbactam etzadroxil in healthy adult participants.	• Dilution-corrected intrapulmonary PK at steady-state o Area under the curve (AUC) from time zero to the last quantifiable sample (AUC_{0-t}) o AUC from time zero to 12 hours (AUC_{0-12}) o Maximum concentration (C_{max}) o Terminal-phase half-life ($t_{1/2}$) in epithelial lining fluid (ELF; if calculable) • Plasma PK at steady-state o AUC_{0-t} o AUC_{0-12} o C_{max} o Minimum concentration (C_{min}) o Time to maximum plasma concentration (T_{max}) o Clearance/bioavailability (CL/F) o Apparent volume of distribution at steady state/bioavailability (V_{ss}/F) o $t_{1/2}$ • Ratios of drug exposure in ELF to plasma using the AUC values for each matrix
Secondary	
To evaluate the safety and tolerability of ceftibuten-ledaborbactam etzadroxil in healthy adult participants.	• Proportion of participants experiencing treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

Objectives	Endpoints
	• Proportion of participants discontinuing study drug due to TEAEs and SAEs
To compare the intrapulmonary concentrations of ceftibuten following administration with ledaborbactam etzadroxil compared with administration alone.	• Comparison of Group 1 vs Group 2 mean ceftibuten intrapulmonary penetration ratios at 4 hours and 12 hours

Overall Design:

This is a Phase 1, open-label, single-center PK study in healthy adult participants between 18 and 55 years of age (both inclusive). Thirty-one participants will each undergo one standard bronchoscopy with bronchoalveolar lavage (BAL) following the fifth dose of the study drug. BAL fluid samples and plasma samples will be collected at designated timepoints to determine the concentrations of ceftibuten, ledaborbactam, and urea.

Brief Summary:

The primary purpose of this study is to assess the intrapulmonary and plasma PK at steady-state in healthy adult participants following multiple dose administration of ceftibuten-ledaborbactam etzadroxil. As a secondary objective, intrapulmonary concentrations of ceftibuten following administration with ledaborbactam will be compared with concentrations following administration of ceftibuten alone.

The duration of the study is expected to be approximately 6 months from the time the first participant signs the informed consent to the last participant's last visit. The maximum duration of participation for each participant will be up to 37 days, including up to 28 days for screening, 5 days (4 nights) of confinement to the clinical research unit, and an outpatient Follow-up visit on Day 8 (±1 day).

Thirty-one participants will each receive a total of 5 doses of ceftibuten-ledaborbactam etzadroxil ([redacted] ceftibuten/[redacted] ledaborbactam etzadroxil) or ceftibuten alone ([redacted]) administered orally every 12 hours. Each participant will undergo one standardized bronchoscopy with BAL following the fifth dose of the study drug. BAL fluid and blood samples will be collected at designated timepoints to determine the intrapulmonary and plasma concentrations of ceftibuten, ledaborbactam, and urea. The number of bowel movements and consistency will be collected and assessed by the CRU staff and recorded from CRU admission through the Follow-up period. Participants will maintain a bowel movement diary during the Follow-up period. Fecal consistency will be captured as hard (stools that are hard, larger or lumpy and/or defecation straining), normal (formed stools, smooth and/or soft and easy to pass), or loose (stools that are mushy or liquid or a mixture of both).

Number of Participants:

A minimum of 31 participants will be enrolled in the study.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are

screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

In Group 1, 25 participants will each receive a total of 5 doses of ceftibuten-ledaborbactam etzadroxil ([redacted] ceftibuten/[redacted] ledaborbactam etzadroxil) administered orally every 12 hours. Each participant will undergo one standardized bronchoscopy with BAL at 1 of 5 designated timepoints following the fifth dose of ceftibuten-ledaborbactam etzadroxil.

In Group 2, an additional 6 participants will each receive a total of 5 doses of [redacted] ceftibuten alone administered orally every 12 hours. Each participant will undergo one standardized bronchoscopy with BAL at 1 of 2 designated timepoints following the fifth dose of ceftibuten.

Data Monitoring/Other Committee: No

1.2. Schedule of Activities

Assessment	Screening	Check-in	Treatment				Follow-up
Study Day[a]	**(Days -28 to -2)**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4 (or ET)**	**Day 8 (± 1 day)**
Informed Consent	X						
Admission to CRU		X					
Discharge from CRU						X	
Inclusion/ Exclusion	X	X					
Medical/Surgical History[b], Smoking and Social History, Demographics	X	X					
Height & Weight[c]	X	X					
Physical Exam[d]	X	X				X	X
Spirometry (FEV1)	X						
Serology (HIV 1/2, HBsAg and HCV)	X						
Urine Drug Screen/Alcohol Breath Test[e]	X	X					
Clinical Laboratory Assessments (Chemistry, Hematology, Coagulation, Urinalysis)[f]	X	X				X	X
Pregnancy Test[g]	X	X					
FSH[h]	X						
12-Lead ECG[i]	X	X					
Vital Signs[j]	X	X	X	X	X	X	X
Study Drug Administration[k]			X	X	X		

Assessment	Screening	Check-in	Treatment				Follow-up
Study Day[a]	**(Days -28 to -2)**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4 (or ET)**	**Day 8 (± 1 day)**
PK blood sample collection[l]			X		X		
Bronchoscopy and BAL samples collection[m]					X		
Blood and BAL sample collection to determine concentration of urea during bronchoscopy[n]					X		
Bowel Movement Assessments[o]		X	X	X	X	X	X
Prior and Concomitant Medication	X	X	X	X	X	X	X
Adverse Events[p]		X	X	X	X	X	X

[a] Screening procedures will be conducted up to 28 days prior to admission to the CRU (Check-in). The Follow-up visit will be conducted on Day 8 (±1 day)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransaminase; BAL = bronchoalveolar lavage; BUN = blood urea nitrogen; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; FEV1 = forced expiratory volume in 1 second; FSH = follicle stimulating hormone; FU = follow-up; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetics; PT = prothrombin time; q12h = every 12 hours

[b] Medical history will include menstrual history and recent sexual activity to decrease the risk for inclusion of a person with an early undetected pregnancy. The number of usual bowel movements per day and their consistency is to be recorded.

[c] Height will be measured at Screening only.

[d] Physical examination will be performed at Screening and Day -1 to include general appearance, skin/subcutaneous tissue, head, ears, nose, throat, neck and thyroid, thorax, lungs, cardiovascular, lymph nodes, abdomen, musculoskeletal, and neurological examinations. Genital, anorectal, and breast examinations will only be performed if medically indicated. A brief physical examination (at a minimum to include respiratory and cardiovascular system) will be conducted on Day 4 (prior to discharge from the CRU) and the Follow-up visit. Any clinically significant changes to the physical examination after the first dose of study drug administration will be recorded as AEs, if they are not signs of another clinical condition that is already listed as an AE.

[e] A urine drug screen to detect cotinine and drugs of abuse (cocaine, cannabinoids, amphetamines, barbiturates, benzodiazepines, methadone, and opiates) and an alcohol breath test will be performed at Screening and Day -1.

[f] Clinical safety laboratory tests at Screening, Day -1, Day 4 (or early discontinuation) and the Follow-up visit will include: hematology: hemoglobin, white blood cell count with differential (including absolute and percent for neutrophils, eosinophils, basophils, lymphocytes and monocytes) and platelet count; Serum Chemistry: ALT, albumin, alkaline phosphatase, AST, total bilirubin (if abnormal, direct bilirubin), BUN, calcium, creatinine, glucose (fasting), potassium, and sodium; Coagulation: PT, aPTT, and INR; Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, urobilinogen; microscopic examination to be performed if abnormal results are obtained for protein and/or blood.

[g] For participants who are persons of childbearing potential not postmenopausal, a serum pregnancy test will be performed at Screening. A urine pregnancy test will be done on Day -1.

[h] FSH will be obtained at Screening on all postmenopausal individuals assigned as females at birth.

[i] ECGs will be performed at Screening and on Day -1. ECGs will be performed before any blood is drawn for clinical laboratory assessments. ECGs will be performed after participants are in supine or semi-Fowler position after a minimum of 5 resting minutes.

[j] Vital signs will be obtained at Screening, Day -1, and the Follow-up visit. On Day 1, and Day 2, vital signs will be collected predose (within 15 minutes) and 2-4 hours after study drug administration of the first dose of the day. On Day 3 (day of bronchoscopy) vital signs will be obtained within 15 minutes prior to the fifth dose of study drug and 30-90 minutes after study drug administration. Participants should be in supine or semi-Fowler position for a minimum of 5 resting minutes prior to collection of vital signs.

[k] In Group 1, a dose of [redacted] ceftibuten ([redacted] capsules) and a dose of [redacted] ledaborbactam etzadroxil ([redacted] capsules) will be coadministered orally q12h for a total of 5 doses of each study drug. Group 2 participants will receive a [redacted] dose of ceftibuten ([redacted] capsules) administered orally q12h for a total of 5 doses. Dose administration should be structured to not provide meals within 2 hours predose or within 2 hours postdose. Participants will refrain from consuming water (other than for administration of the study medication) from 1 hour predose until 1 hour postdose.

[l] Blood samples will be collected for drug assay within 2 hours before the first dose on Day 1 and within 15 minutes before (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the fifth dose of study drug.

[m] Group 1 participants will undergo one standardized bronchoscopy and BAL at one of the following time-points 2, 4, 6, 8 and 12 hours (5 participants at each time-point) after the fifth dose of ceftibuten-ledaborbactam etzadroxil. Participants in Group 2 will undergo one standardized bronchoscopy and BAL at one of the following time-points 4 and 12 hours (3 participants each) after the fifth dose of ceftibuten.

[n] A blood sample to determine the concentration of urea will be obtained at each BAL timepoint at the start of the second instillation of BAL. Aliquots of BAL fluid will be saved for BAL urea determination from the BAL fluid collected after the first instillation and after pooling the 2nd, 3rd, and 4th instillations of BAL.

[o] All bowel movements will be recorded from CRU admission through the Follow-up Period. Participants will be given a diary to record their daily bowel movements during the Follow-up Period.

[p] Adverse events will be collected from Day -1 through the FU visit.

2. INTRODUCTION

Venatorx is developing ledaborbactam etzadroxil, an inactive prodrug of the active β-lactamase inhibitor parent, ledaborbactam, in combination with ceftibuten (a β-lactam antibiotic) for treatment of complicated and uncomplicated urinary tract infections. Both diseases have recently experienced an alarming increase in incidence due to β-lactamase-producing pathogens.

2.1. Study Rationale

This study is being conducted to compare the intrapulmonary pharmacokinetics (PK) to the plasma PK of ceftibuten and ledaborbactam to inform dose selection for a future Phase 3 study evaluating the efficacy of ceftibuten-ledaborbactam etzadroxil for the treatment of lower respiratory tract infections.

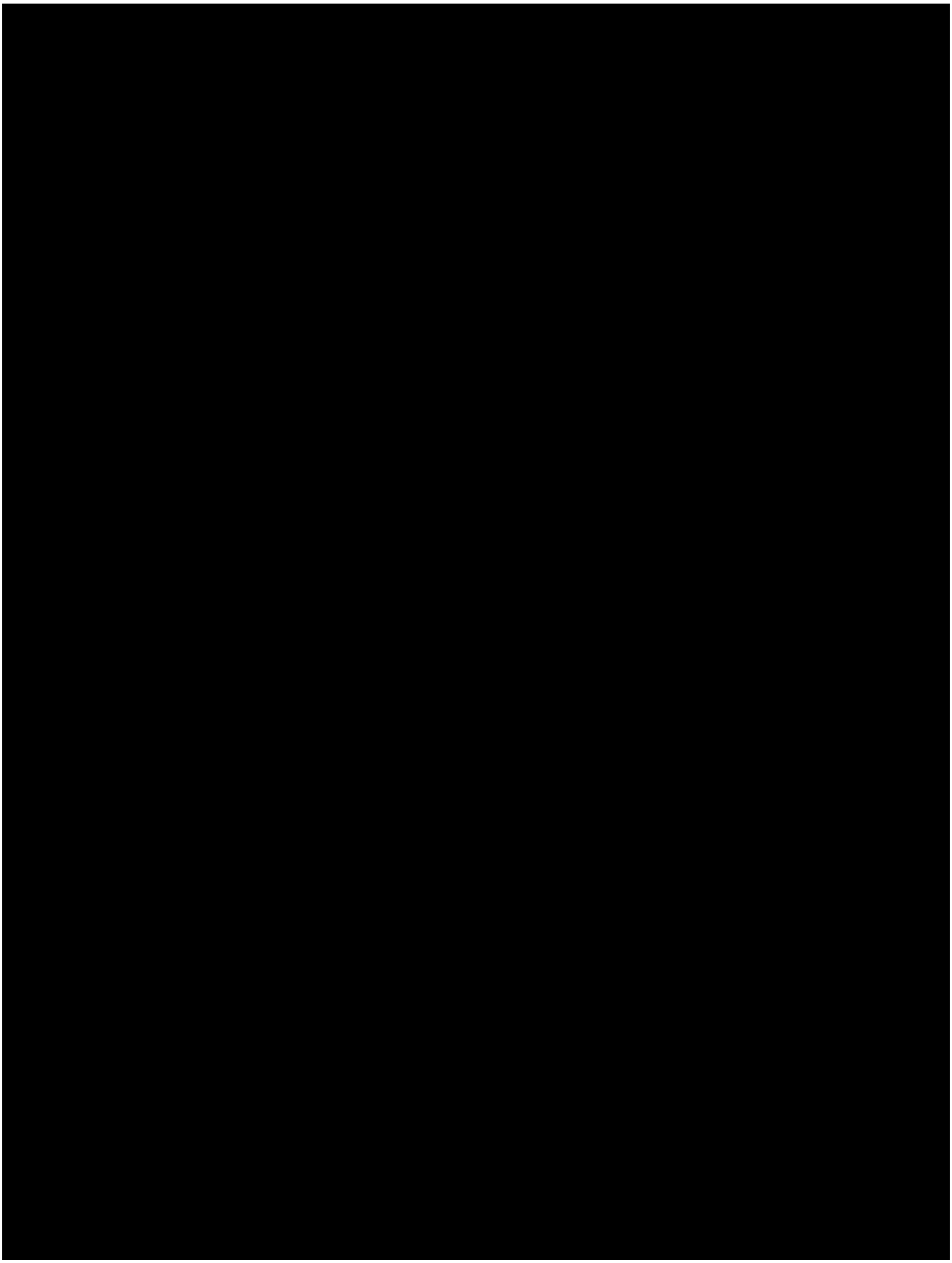
2.2. Background

Ceftibuten, an oral broad-spectrum, third-generation cephalosporin antibiotic, was approved by the United States Food and Drug Administration in 1995 under the tradename Cedax® for the treatment of acute otitis media, acute bacterial exacerbations of chronic bronchitis, acute maxillary sinusitis, pharyngitis, and tonsillitis at a dose of 400 mg once daily for adults. Ceftibuten was subsequently approved for children 6 months through 11 years of age at a dose of 9 mg/kg (up to 400 mg/day). More information about the safety and efficacy of ceftibuten can be found in the Cedax® package insert (PI) (Pernix Therapeutics 2011). Ceftibuten is approved for urinary tract infections (UTIs) in addition to upper and lower respiratory tract infections in several countries in Europe.

Ledaborbactam etzadroxil (VNRX-7145) is the inactive prodrug of the novel broad-spectrum active β-lactamase inhibitor parent, ledaborbactam (VNRX-5236). Ceftibuten-ledaborbactam etzadroxil has the potential to address an urgent, unmet medical need for new orally administered agents to treat serious infections caused by drug-resistant Enterobacterales expressing extended-spectrum beta-lactamases and serine carbapenemases. Therefore, ceftibuten-ledaborbactam etzadroxil has the potential to be used as an oral step-down therapy for these drug resistant infections for indications including pneumonia.

Refer to the Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of ledaborbactam etzadroxil, ledaborbactam, and ceftibuten.







2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ceftibuten-ledaborbactam etzadroxil may be found in the IB and ceftibuten PI.

2.3.1. Risk Assessment

There is no expected clinical benefit for the healthy participants who will participate in this study. The information obtained in this study will be used for the further clinical development of ceftibuten-ledaborbactam etzadroxil.

3. OBJECTIVES AND ENDPOINTS

The primary purpose of this study is to assess the plasma and intrapulmonary PK at steady-state in healthy adult participants following multiple dose administration of ceftibuten-ledaborbactam etzadroxil.

Objectives	Endpoints
Primary	
To evaluate the steady-state intrapulmonary PK and plasma PK of ledaborbactam and ceftibuten following administration of ceftibuten-ledaborbactam etzadroxil in healthy adult participants.	• Dilution-corrected intrapulmonary PK at steady-state o Area under the curve (AUC) from time zero to the last quantifiable sample (AUC_{0-t}) o AUC from time zero to 12 hours (AUC_{0-12}) o Maximum concentration (C_{max}) o Terminal-phase half-life ($t_{1/2}$) in epithelial lining fluid (ELF; if calculable) • Plasma PK at steady-state o AUC_{0-t} o AUC_{0-12} o C_{max} o Minimum concentration (C_{min}) o Time to maximum plasma concentration (T_{max}) o Clearance/bioavailability (CL/F) o Apparent volume of distribution at steady state/bioavailability (V_{ss}/F) o $t_{1/2}$ • Ratios of drug exposure in ELF to plasma using the AUC values for each matrix
Secondary	
To evaluate the safety and tolerability of ceftibuten-ledaborbactam etzadroxil in healthy adult participants.	• Proportion of participants experiencing treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Proportion of participants discontinuing study drug due to TEAEs and SAEs
To compare the intrapulmonary concentrations of ceftibuten following administration with ledaborbactam etzadroxil with administration alone.	• Comparison of Group 1 vs Group 2 mean ceftibuten intrapulmonary penetration ratios at 4 hours and 12 hours

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, single-center PK study in healthy adult participants between 18 and 55 years of age (both inclusive). The study will be conducted at one clinical site in the United States. The primary purpose of this study is to assess the intrapulmonary and plasma PK at steady-state in healthy adult participants following multiple dose administration of ceftibuten-ledaborbactam etzadroxil. As a secondary objective, intrapulmonary concentrations of ceftibuten following administration with ledaborbactam will be compared with concentrations following administration of ceftibuten alone.

In Group 1, 25 participants will each receive a total of 5 doses of ceftibuten-ledaborbactam etzadroxil ([redacted] ceftibuten/[redacted] ledaborbactam etzadroxil) administered orally every 12 hours (q12h). Following the fifth dose of ceftibuten-ledaborbactam etzadroxil, each participant will undergo one standardized bronchoscopy with bronchoalveolar lavage (BAL) at one of 5 designated timepoints (2, 4, 6, 8, and 12 hours; n=5 participants/timepoint).

In Group 2, an additional 6 participants will each receive a total of 5 doses of [redacted] ceftibuten alone administered orally q12h. Following the fifth dose of ceftibuten, each participant will undergo one standardized bronchoscopy with BAL at one of two designated timepoints (4 and 12 hours; n=3 participants/timepoint).

The number of bowel movements and consistency will be collected and assessed by the CRU staff and recorded from CRU admission through the Follow-up period for both Groups. Participants will maintain a bowel movement diary during the Follow-up period. Fecal consistency will be captured as hard (stools that are hard, larger or lumpy and/or defecation straining), normal (formed stools, smooth and/or soft and easy to pass), or loose (stools that are mushy or liquid or a mixture of both).

The Investigator will determine which participants are assigned to each of the groups and specific bronchoscopy timepoints. Participants who do not complete the bronchoscopy will be replaced.

Blood samples to determine plasma concentrations of ceftibuten, ledaborbactam (Group 1 only), and urea will be collected at the designated timepoints.

4.2. Scientific Rationale for Study Design

The ELF has been advocated as an important infection site for common extracellular pathogens of lower respiratory tract infections. Studies with bronchoscopy and BAL have been performed to determine the intrapulmonary penetration of antibiotics into the ELF (Drwiega 2022); (Rodvold 2011); (Baldwin 1992); (Rodvold 2017).

4.2.1. Participant Input into Design

The design of the protocol did not involve any participant input.

4.3. Justification for Dose

The doses of ceftibuten and ledaborbactam etzadroxil and the dose regimen being used in this study are anticipated to be the therapeutic doses that will be studied in a Phase 3 clinical trial.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of any protocol deviation to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Voluntarily signed and dated the Institutional Review Board (IRB) approved Informed Consent Form (ICF) prior to performing any study-specific screening procedures.
2. Healthy adult male or female, between 18 and 55 years of age (both inclusive) at the time of screening.
3. Willing and able to comply with all study assessments, confinement to the clinical research unit (CRU) and restrictions outlined in the protocol.
4. Body mass index (BMI) ≥18 and ≤32 kg/m^2 and weight >50.0 kg (110 lbs) for men and ≥45.0 kg (99 lbs) for women.
5. Forced expiratory volume in 1 second (FEV1) of at least 80% of predicted value at Screening.
6. Laboratory values meeting defined laboratory ranges using the criteria outlined in Table 1 at Screening and Day -1. A laboratory parameter with a required value may be repeated once at Screening or Day -1 to confirm a plausible alternative explanation to an abnormal value.
7. Suitable venous access for blood sampling.
8. Non-smoker, non-vaper (with no use of tobacco, nicotine, or marijuana-containing products, in any form within 14 days prior to Screening), as documented by history.
9. Participants assigned as male at birth who have not undergone a surgical procedure resulting in sterilization are eligible to participate if they agree to the following during the study period and for at least 90 days after study drug administration:

   - Refrain from donating sperm, be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), and agree to remain abstinent.

   OR

   - Agree to use a male condom when having sexual intercourse with a person of childbearing potential who is currently not pregnant.

10. A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

    - Is a person of non-childbearing potential as defined in Section 10.4.

    OR

    - Is a person of childbearing potential (POCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the

study period and for at least 90 days after the last dose of study drug. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study drug. A POCBP must have a negative pregnancy test at Screening and Day -1.

11. Ability and willingness to abstain from foods and beverages containing poppy seeds, grapefruit, or Seville oranges within 48 hours prior to Check-in (Day -1) until the end of the study (Day 8 ±1 day).
12. Ability and willingness to abstain from alcohol from 48 hours prior to Check-in (Day -1) until the end of the study (Day 8 ±1 day).
13. Ability and willingness to not engage in strenuous physical activity, sunbathing, and contact sports at least 48 hours prior to Check-in (Day -1) until the end of the study (Day 8 ±1 day).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. History of any hypersensitivity reaction following administration of a cephalosporin, penicillin, or other β-lactam antibacterial drug or any component of the ceftibuten or ledaborbactam etzadroxil formulation.
2. History of hypersensitivity to any medications (including topical medications) used during the bronchoscopy.
3. History or presence of significant oncologic, cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, vascular, or neurological disease (including seizure disorders), including any acute illness or surgery within the past 3 months determined by the Investigator to be clinically relevant.
4. Recent history (within 6 months) of known or suspected *Clostridioides difficile* infection.
5. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is employed at the CRU, Contract Research Organization (CRO) or Sponsor staff directly involved with this trial.
6. Presence of symptoms consistent with respiratory infections at Screening or Check-in (Day -1).
7. ECG with QT interval corrected for heart rate using the Fridericia's method (QTcF) ≥450 msec for males and ≥470 msec for females at Screening or Check-in (Day -1) or presence of any other clinically significant ECG findings according to the Investigator. One repeat test at Screening and/or Day -1 is permitted to confirm a plausible alternative explanation to an abnormal value.
8. Recent history of alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink = 10 grams of alcohol). Alcohol consumption will be prohibited 48 hours before admission to the CRU and throughout the entire study.

9. All prescription and over-the-counter (OTC) medication, health supplements, and herbal remedies (eg, St. John's Wort extract) must have been stopped at least 14 days prior to first dose. Exceptions are outlined in Section 6.8.
10. Donation of blood or plasma within 30 days prior to Check-in (Day-1), or loss of whole blood of more than 500 mL within 30 days prior to Check-in (Day-1), or receipt of a blood transfusion within 1 year of study enrollment.
11. Participated in a clinical study involving administration of an investigational drug (new chemical entity) in the past 30 days (90 days for an injectable biological agent) prior to screening.
12. Female who is pregnant, lactating, or plans to become pregnant during this trial or within 90 days after the last dose of study drug.
13. Male with a female partner who is pregnant or lactating during this trial or planning to attempt to become pregnant during this trial or within 90 days after the last dose of study drug.

Table 1: Permitted Laboratory Values at Screening and/or Day -1 for Inclusion

Parameter	Inclusion Values
Tested at Screening Only	
Serology	
HBsAg	Negative
anti-HCV antibody	Negative
anti-HIV 1/2 antibodies	Negative
Postmenopausal individuals assigned as females at birth	
FSH	Value per local lab range
Tested at Screening and Baseline	
Drug (urine) and Alcohol Screen (breath)	
Cannabinoids	Negative
Amphetamines	Negative
Opiates	Negative
Methadone	Negative
Cocaine	Negative
Benzodiazepines	Negative
Barbiturates	Negative
Alcohol	Negative
Cotinine	Negative

Parameter	Inclusion Values
Pregnancy Test in POCBP	
Serum β-hCG (Screening)	Negative
Urine hCG (Day -1)	Negative
Coagulation	
INR	≤1.2 ULN
aPTT	≤1.2 ULN
Chemistry	
Alkaline Phosphatase	≤2xULN
ALT/SGPT	≤1.5×ULN
AST/SGOT	≤1.5×ULN
Bilirubin, total	≤1.5×ULN
BUN	≤ULN
Creatinine	≤ULN
Hematology	
Hemoglobin	>0.85×LLN
WBC	*For participants of African descent:* ≥2700 × 10^9/L for females and ≥2500 × 10^9/L for males with medical history of WBC count in a similar range in the absence of a clinical cause *All others:* 0.75×LLN and ≤1.2×ULN
Absolute neutrophil count	0.75×LLN or ≥1000 10^9/L (participants of African descent only)
Platelet count	>0.9×LLN
Urinalysis	
Protein	Negative or trace (if specific gravity is >1.015)
Blood	Negative

β-hCG = β-human chorionic gonadotropin, ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase, BUN = blood urea nitrogen; FSH = follicle-stimulating hormone, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV = human immunodeficiency virus, INR = international normalized ratio, LLN = lower limit of normal, POCBP = person of childbearing potential, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamate-pyruvate transaminase; ULN = upper limit of normal, WBC = white blood cell; WNL = within normal limit

Normal limits based on laboratory defined ranges (adjusted for age, gender, and race as appropriate)

Any parameter not meeting defined entry criteria may be retested once in instances of suspected lab error or medical justification for a transient out of range value

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants are not allowed to consume any foods containing poppy seeds, grapefruit, or Seville oranges within 48 hours (2 days) prior to Check-in (Day -1) until the end of the study (Day 8 ±1 day). Dose administration should be structured to not provide meals within 2 hours predose or within 2 hours postdose. Participants will refrain from consuming water (other than for administration of the study medication) from 1 hour predose until 1 hour postdose.

5.3.2. Caffeine, Alcohol, and Tobacco

The use of alcohol is not allowed from 48 hours prior to Check-in (Day -1) until the end of the study (Day 8 ±1 day).

Tobacco- and marijuana-containing products are not allowed from Check-in (Day -1) until the end of the study (Day 8 ±1 day).

5.3.3. Activity

Strenuous exercise, contact sports, and sunbathing are not allowed within 48 hours (2 days) prior to Check-in (Day -1) until the Follow-up visit.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened with approval of the Sponsor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

In Group 1, a [redacted] dose of ceftibuten ([redacted] capsules) with a [redacted] dose of ledaborbactam etzadroxil ([redacted] capsules) will be coadministered orally q12h for a total of 5 doses of each study drug.

In Group 2, a [redacted] dose of ceftibuten ([redacted] capsules) will be administered orally q12h for a total of 5 doses.

Ledaborbactam etzadroxil and ceftibuten will be administered orally with approximately 240 mL of room-temperature water.

Arm Name	**Group 1**		**Group 2**
Intervention Name	Ledaborbactam etzadroxil	Ceftibuten	Ceftibuten
Type	Drug	Drug	Drug
Dose Formulation	Capsule	Capsule	Capsule
Unit Dose Strength	[redacted] capsules	[redacted] capsules	[redacted] capsules
Dosage Level	[redacted] capsules	[redacted] capsules	[redacted] capsules
Route of Administration	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental
Investigational Medicinal Product and Non-Investigational Medicinal Product	Investigational product	Investigational product	Investigational product
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Study drug will be provided in bottles. Each bottle will be labeled as required per country requirement	Study drug will be provided in blister packs. Each blister pack will be labeled as required per country requirement	Study drug will be provided in blister packs. Each blister pack will be labeled as required per country requirement

6.2. Preparation/Handling/Storage/Accountability

Capsules containing [redacted] ledaborbactam etzadroxil and capsules containing [redacted] ceftibuten will be supplied by the Sponsor (or designee), along with the batch/lot numbers and

certificates of analysis. Ledaborbactam etzadroxil will be provided in 30-count bottles and ceftibuten will be provided in 10-count blister packs.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention. Both study drugs should be stored protected from light at 2° to 8°C. Investigational medicinal products will be stored at the study site in a location that is locked with restricted access.

Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The study drugs will be transferred from bulk supplies into the participant's dose container by qualified clinical staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Refer to the Pharmacy Manual, IB, and Cedax® PI for additional information (Pernix Therapeutics 2011).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, non-comparative study; randomization will not be used.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site staff will examine each participant's mouth and hands to ensure that the study intervention was ingested.

6.5. Dose Modification

No dose modifications are allowed.

6.6. Continued Access to Study Intervention After the End of the Study

No study intervention will be available after the end of the study.

6.7. Treatment of Overdose

For this study, more than 2 doses in a period of 24 hours will be considered an overdose. Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Contact the Sponsor or designee within 24 hours.
- Evaluate the participant to determine, in consultation with the Sponsor or designee, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until the Follow-up visit.
- Document the quantity of the excess dose as well as the duration of the overdose.
- Overdose is not necessarily an AE, but if the consequences of the overdose result in a serious or nonserious AE, they should be reported as such, separate from the overdose.

6.8. Concomitant Therapy

All prescribed medication, OTC medication, vitamin preparations, other food supplements, or herbal medications (eg, St. John's wort) must have been stopped from 14 days prior to first dose.

An exception is made for acetaminophen. From admission to the CRU onwards, the PI or qualified designee may permit a limited amount of acetaminophen (<3 grams daily) for the treatment of headache or any other pain. An exception is also made for hormonal contraceptives, which are allowed throughout the study. Additionally, medications that do not have a systemic or gastrointestinal effect (eg, topical medications such as ketoconazole cream for antifungal infections, or ophthalmic drops used to treat seasonal allergies) may be used at the discretion of the PI or qualified designee and after consultation with the Sponsor. Other medications to treat AEs may only be prescribed if deemed necessary by the PI or qualified designee.

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the electronic case report form (eCRF) along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Sponsor Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety assessments. See the Schedule of Assessments (SoA; Section 1.2) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

A participant will be withdrawn from dosing if any of the following criteria are met:

- Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects participant safety as determined by the Investigator (or designee);
- Noncompliance with the study restrictions that might affect participant safety or study assessments/objectives, as considered applicable by the Investigator (or designee); or
- Any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants participant withdrawal.

7.1.1. Temporary Discontinuation

Temporary discontinuation is not permitted in this study.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

If a participant is withdrawn from the study, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the participant's source documents and the eCRF. If a participant is withdrawn from the study, efforts will be made to perform all early termination assessments, if possible. Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the participant is in-house, these procedures should be performed before the participant is discharged from the clinic. The Investigator (or designee) may also request that the participant return for an additional Follow-up visit. All withdrawn participants will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

The participant will be permanently discontinued both from the study intervention and from the study at that time. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Participants may be replaced, or additional participants enrolled, to ensure the minimum number of PK evaluable participants per group (see Section 9.2). Participants may be replaced only

following discussion between the Investigator and the Sponsor. The decision regarding the replacement of participants will be documented.

7.2.1. Individual Halting Criteria

If any of the following is observed while a participant is enrolled, further dosing of the individual participant may be discontinued after discussion with the Sponsor due to the following reasons:

- A study drug related SAE or study drug related Grade 3 AE (ie, not clearly related to baseline comorbidities or medical history);
- An increase in serum creatinine >0.3 mg/dL or >150% from participant's baseline;
- A confirmed presence of abnormal renal tubular epithelial cell casts in the urinalysis;
- Any non-serious AE that, in the opinion of the Investigator, warrants discontinuation of study medication for the participant's well-being;
- Pregnancy; or
- Termination of the study by the Sponsor.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for the scheduled Follow-up visit on Day 8 (±1 day) and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as described in Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.2). Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to participant safety. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.2), is essential and required for study conduct.

8.1. Administrative and General Procedures

The Investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICF before performing any study-specific procedures. See Section 10.1.3 for additional information on the Informed Consent process.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.2).

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1.1. Medical History/Demography

Medical history, demographic data including name, sex, age, race, ethnicity, bowel movement frequency and consistency, and history of alcohol, tobacco, and marijuana-containing product use will be recorded.

8.2. Efficacy Assessments

Not applicable

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.2).

8.3.1. Physical Examinations

Physical examinations will be performed at the times indicated in the SoA (Section 1.2). Physical examinations may be repeated, if clinically indicated. Any clinically significant changes to the physical examination after the first dose of study drug administration will be recorded as AEs.

A complete physical examination will include, at a minimum, assessments of the skin/subcutaneous tissue, head, ears, nose, throat, neck and thyroid, thorax, lungs,

cardiovascular, lymph nodes, abdomen, musculoskeletal, and neurological systems. Height and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the respiratory and cardiovascular systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

Blood pressure, pulse rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the SoA (Section 1.2). Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range (see Table 4).

Participants must be supine or semi-Fowler for at least 5 resting minutes before blood pressure and pulse rate measurements.

8.3.3. Electrocardiograms

A 12-lead ECG will be obtained as outlined in the SoA (Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

ECGs will be performed before any blood is drawn for clinical laboratory assessments. ECGs will be performed after participants are in supine or semi-Fowler position after a minimum of 5 resting minutes.

ECGs may be repeated, if clinically indicated.

8.3.4. Clinical Safety Laboratory Assessments

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the SoA (Section 1.2). Clinical laboratory evaluations are listed in Table 3 in Section 10.2. The Investigator (or designee) will perform a clinical assessment of all clinical laboratory data. Additional assessments that are part of predetermined laboratory-directed panels may be obtained but will not be part of the safety analysis.

Clinical laboratory tests may be repeated, if clinically indicated. All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.2).

8.3.5. Pregnancy Testing

For all POCBP, a pregnancy test will be performed at the times indicated in Section 1.2. A serum pregnancy test should be performed at Screening; a urine pregnancy test will be done on Day -1.

A follicle-stimulating hormone (FSH) value will be obtained at Screening on all postmenopausal individuals assigned as females at birth.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Study intervention is not considered to be a central nervous system-active intervention.

8.3.7. Bowel Movement Assessments

CRU staff will collect and assess participants' bowel movements each day starting on the day of CRU admission through the Follow-up period. Participants will maintain a bowel movement diary during the Follow-up period. The following information will be recorded in the source documentation and eCRF:

- Total number of bowel movements per calendar day
- Fecal consistency will be captured as hard (stools that are hard, larger or lumpy and/or defecation straining), normal (formed stools, smooth and/or soft and easy to pass), or loose (stools that are mushy or liquid or a mixture of both).

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs including SAEs will be collected from Check-in until the Follow-up visit at the time points specified in the SoA (Section 1.2).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

All AEs that occur from Check-in through the Follow-up visit, whether or not they are related to the study, must be recorded on the AE eCRF page. Follow-up of AEs will continue until resolution, stabilization, or death. Every reasonable effort will be made to follow up with participants who have AEs. Any participant who has an ongoing AE at the Follow-up visit will be followed, where possible, until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. In case of ongoing AEs at database closure, the data recorded at the time of database closure will be used in the statistical analysis. The follow-up of the AE will be documented in source documents and will be described in the final clinical study report (CSR) only if considered relevant by the PI.

All SAEs that occur from Check-in through the Follow-up visit, whether or not they are related to the study, must be recorded on the SAE form. SAEs that continue beyond the normal collection period (ie, are ongoing at the time a participant exits the study) will be followed until resolution or until stabilized with sequelae. SAEs that begin after the participants' participation in the study is complete, but that the PI considers to be related to study drug, should be reported at any time.

Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

All SAEs (related and unrelated) will be recorded from Check-in until the Follow-up visit. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to the Sponsor within 24 hours of the first awareness of the event. In addition, if the Investigator learns at any time of an SAE which is believed to be related to the study treatment, then this must be reported to the Sponsor, even if more than 30 days have elapsed since the last dose of study treatment.

The PI or the clinical site personnel will notify the ICON Pharmacovigilance and Safety Services (Table 2) and the Sponsor of all SAEs regardless of relationship to the investigational drug. The PI will provide the initial notification by sending a completed "Safety Report Form," which must include the PI's assessment of the relationship of the event to investigational drug and must be signed by the PI. The Sponsor will review and assess the SAE for expectedness and relatedness.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the ICON Pharmacovigilance and Safety Services (Table 2) and communicated to the Sponsor.

Table 2: Emergency Contact Information

ICON Pharmacovigilance and Safety Services
Email (primary method): CHOSafety@iconplc.com icon-mads@iconplc.com Fax (secondary method): +1-888-772-6919 or +1-434-951-3482 +1-215-616-3096

It is the PI's responsibility to notify the IRB of all SAEs that occur at his or her site.

Venatorx Pharmaceuticals is responsible for notifying the relevant regulatory authorities of certain events. Venatorx is responsible for submitting the SAE to the Division of Microbiology and Infectious Disease (DMID) medical monitor and the DMID clinical project manager as soon as possible, but no later than 24 hours after learning of an SAE.

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

Should a pregnancy occur, it must be reported and recorded on the pregnancy report form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and considered as SAEs. Elective abortions without complications should not be reported as AEs.

- Details of all pregnancies in participants and, if indicated, female partners of participants assigned male at birth will be collected after the start of study intervention and until 90 days after the last dose of study drug.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant partner and the neonate and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant partner he or she may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.6. Cardiovascular and Death Events

Not applicable to this study.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable to this study.

8.4.8. Adverse Events of Special Interest

Not applicable to this study.

8.5. Pharmacokinetics

8.5.1. Bronchoscopy and Bronchoalveolar Lavage

BAL samples will be collected at various timepoints to determine the concentrations of urea, ceftibuten, and ledaborbactam (Group 1 only) in BAL.

- Each participant in Group 1 (5 participants at each timepoint) will undergo one standardized bronchoscopy with BAL at one of the designated time points: 2 (±5 min), 4 (±5 min), 6 (±5 min), 8 (±5 min), and 12 (±5 min) hours after the fifth dose of ceftibuten-ledaborbactam etzadroxil.
- Each participant in Group 2 (3 participants at each timepoint) will undergo one standardized bronchoscopy with BAL at one of the designated timepoints: 4 (±5 min) and 12 (±5 min) hours after the fifth dose of ceftibuten alone.

Four 50-mL aliquots of sterile 0.9% normal saline will be instilled into the lung lobe, and each specimen will be immediately aspirated and placed in ice.

- The aspirate from the first 50-mL instillation will be collected separately (BAL 1). The volume of BAL 1 will be measured and recorded. The volume of BAL 1 will be immediately centrifuged at 400 × *g* for 5 min. The supernatant and cells will be separated. Aliquots from the supernatant will be collected and stored for measurement of ceftibuten and ledaborbactam (Group 1 only) in BAL 1. A single aliquot of supernatant will be collected and stored for measurement of urea in BAL 1. All aliquots of supernatant will be frozen at ≤-70°C until the assays are performed.
- The aspirates recovered from the second, third, and fourth instillations will be pooled (BAL 2). The volume of BAL 2 will be measured and recorded. The volume of BAL 2 will be immediately centrifuged at 400 × *g* for 5 min. The supernatant and cells will be separated. Aliquots from the supernatant will be collected and stored for measurement of ceftibuten and ledaborbactam (Group 1 only) in BAL 2. A single aliquot of supernatant will be collected and stored for measurement of urea in BAL 2. All aliquots of supernatant will be frozen at ≤-70°C until the assays are performed.

The time of each instillation of sterile saline aliquots and the time of BAL sample collection will be recorded in the eCRF. Detailed instructions for the processing and handling of BAL samples are provided in a laboratory manual.

8.5.2. Blood Sample Collection for Drug and Urea Assay

Blood samples will be collected to determine plasma concentrations of urea, ceftibuten and ledaborbactam (Group 1 only) with validated assays. Samples will be collected at the following timepoints for ceftibuten and ledaborbactam assays (Group 1 only): within 2 hours of the first dose of the study drug on Day 1 (predose), within 15 minutes prior to the fifth dose (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after the fifth dose of the study drug.

In Group 1, 2 blood samples will be collected by venipuncture or cannulation at each timepoint. Approximately 2 mL will be collected in KOx-NaF tubes for ledaborbactam assays and another 2 mL will be collected in K_2-EDTA tubes for ceftibuten assays. For Group 2, a single 2 mL sample will be collected at each timepoint in K_2-EDTA tubes for ceftibuten assays.

A blood sample to determine the concentration of urea will be obtained at the start of the second instillation.

Clinical staff is encouraged to take other blood samples for PK analysis at the scheduled time point; however, deviations from the scheduled sample times are not considered protocol

deviations. The exact time and date of the blood draw must be recorded using an unambiguous format such as DD MON YYYY and HH:MM using a 24-hour clock.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The blood samples to determine the plasma concentrations of ceftibuten and ledaborbactam are to be stored upright in a ≤-20°C freezer within 60 minutes of collection. The blood samples to determine plasma concentration of urea are to be stored upright in a -70°C freezer within 60 minutes of collection.

Genetic analyses will not be performed on these samples.

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics and medical resource utilization are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal statistical hypothesis testing will be performed in this study.

9.2. Sample Size Determination

The sample size of 25 participants for Group 1 (5 per group at 5 timepoints) is based on the desire to obtain sufficient PK data to achieve the primary objective of the study. The sample size of 6 participants for Group 2 (3 per group for at 2 timepoints) is considered sufficient to achieve the secondary objective to the study.

9.3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Safety	All participants who received at least one dose of the study drug will be included in the safety summary.
Pharmacokinetic evaluable	Pharmacokinetic evaluable population: All participants who have received at least one dose of the study drug and provided at least one evaluable plasma or BAL concentration.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

This is primarily a descriptive study assessing the concentrations of ceftibuten and ledaborbactam in plasma compared with ELF. No formal statistical hypothesis testing will be performed in this study.

Noncompartmental PK analysis will be performed by using the Phoenix WinNonlin (version 8.1 or higher; Certara, Princeton, N.J.). Details of proposed data and PK analysis and statistical methods will be provided in the SAP. Efficacy will not be assessed in this study, and no interim analyses are planned.

9.4.2. Safety Analysis

Descriptive statistics will be calculated and summarized for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

A by-participant TEAE data listing, including verbatim term, preferred term (PT), treatment, severity, and relationship to treatment, will be provided. TEAEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) by system organ class

(SOC) and PT, classified from verbatim terms. The incidence and frequency of AEs, and SAEs, will be summarized by severity and relationship. Prior and concomitant medications will be classified according to the World Health Organization Drug dictionary.

9.4.3. Pharmacokinetic Analysis

For Group 1, mean and individual plasma and ELF concentration-time profiles curves will be generated for ceftibuten and ledaborbactam, as appropriate. Plasma and ELF concentrations and PK parameters, including ELF to free plasma ratios, will be determined for each participant, and summarized. Each ELF concentration will be corrected for dilution based on ELF/plasma urea concentration ratios. Since only total concentrations of drugs are measured in plasma, free plasma drug concentrations of ceftibuten and ledaborbactam will be calculated using the percentage of protein binding obtained from a different study. It will be assumed there is no protein binding in ELF. Concentrations for each analyte will be tabulated for each participant together with descriptive statistics: mean, standard deviation, geometric mean, percent geometric coefficient of variation (%GCV), coefficient of variation, minimum, maximum, and median values, and the number of observations.

The intrapulmonary penetration ratios will be determined with AUC. $AUC_{0\text{-}12}$ will be determined for the comparison of systemic exposure in plasma and ELF of each analyte. For concentrations in plasma, the means from each available sampling time will be used to estimate an $AUC_{0\text{-}12}$. The mean concentrations from bronchopulmonary sampling times will be used to estimate the $AUC_{0\text{-}12}$ of ELF. The 12-h sampling time will also be used as a value at time zero for determining the area term of ELF. Penetration ratios will be calculated as $AUC_{ELF}/fAUC_{plasma}$.

Noncompartmental PK parameters (eg, C_{max}, C_{min}, $t_{½}$, $AUC_{0\text{-}t}$, CL/F) based on total (measured) and free (calculated) plasma concentrations of ceftibuten and ledaborbactam will also be determined for each individual participant for Group 1. Mean graphical presentation of the data will be reported.

For Group 2, individual total and free ceftibuten plasma and ELF concentrations as well as the intrapulmonary penetration ratios of the ceftibuten concentration in ELF to plasma will be tabulated along with descriptive statistics (mean, standard deviation, geometric mean, %GCV, coefficient of variation, minimum, maximum, and median values, and the number of observations) for each timepoint. Comparison of Group 1 vs Group 2 mean ceftibuten ELF concentration ratios at 4 hours and 12 hours will be summarized.

9.5. Interim Analysis

No interim analysis is planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

In the event a pregnancy occurs in the partner of a male participant within 90 days of dosing, informed consent will be obtained from the female partner to collect information about the outcome of the pregnancy.

10.1.4. Data Protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Early Safety Data Review

Venatorx Medical Sciences is responsible for regularly monitoring safety issues emerging from study participation. The Venatorx medical monitor is also responsible for periodically informing the DMID medical monitor of AEs and other safety issues.

Identification of urgent safety signals or urgent safety issues (eg, a halting rule [Section 7.2.1] is met) that may arise during the study should be promptly escalated to the DMID medical monitor by Venatorx. The urgent safety signal or safety issue is assessed by Venatorx Medical Sciences and the DMID medical monitor to determine the appropriate course of action to ensure participant safety.

10.1.6. Dissemination of Clinical Study Data

As this is a Phase 1 study, Venatorx is not obligated to disseminate results of this study.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Guidance on completion of CRFs will be provided in the eCRF Completion Guidelines.

The Investigator must permit study-related monitoring visits conducted by the Sponsor, National Institute of Allergy and Infectious Disease (NIAID) staff, or their representatives, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Clinical Management Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data. The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Clinical Management Plan. The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the site initiation visit and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If any of the following events occur, enrollment and dosing for all participants will be suspended until the event is assessed by Venatorx Medical Sciences and the DMID medical monitor:

- One study drug related SAE (ie, not clearly related to baseline comorbidities or medical history);
- Two participants have a study drug related Grade 3 systemic or laboratory AE in the same MedDRA high level term (HLT);
- Two participants have an increase in serum creatinine >0.3 mg/dL or >150% from participants’ baseline;

- Two participants have confirmed presence of abnormal epithelial cell casts in the urinalysis; or
- Two or more participants discontinued from study drug due to non-serious systemic or laboratory AEs, where the 2 events occurred in the same HLT.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

The primary publication associated with this study will be coordinated through the Sponsor. The Sponsor will provide data access to the Investigators and authors. Authorship will be determined by mutual agreement and as established by the International Committee of Medical Journal Editors. If additional publications result from this activity and are not directed by the Sponsor, then the Investigator agrees to submit all abstracts, posters/presentations, and manuscripts to the Sponsor before submission. The Sponsor shall have a review period of 30 days to provide comments and may request an additional 90 days in order to protect proprietary information.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 3 will be performed by the local laboratory. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Investigators must document their review of each laboratory safety report.

Table 3: Protocol-Required Safety Laboratory Tests

Panel	Parameters
Coagulation	aPTT INR PT
Chemistry	ALT Albumin Alkaline phosphatase AST Bilirubin, total (if abnormal, direct bilirubin) BUN Calcium Creatinine Glucose (fasting) Potassium Sodium
Hematology	Hemoglobin Platelets WBC count with differential (absolute and percentage of neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
Urinalysis	pH

Panel	Parameters
	Specific gravity Protein Glucose Ketones Bilirubin Blood Urobilinogen Microscopic examination[a]
Serology	Anti-hepatitis B surface antibody Anti-hepatitis B core antibody Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies
Hormone Panel (females only)	Follicle-stimulating hormone Serum pregnancy test (human chorionic gonadotropin)[b]

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HIV = human immunodeficiency; INR = international normalized ratio; PT = prothrombin time; WBC = white blood cell

[a] To be performed only if abnormal results are obtained for protein and/or blood

[b] In serum at Screening; may use urine test on Day -1

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), if they are not signs of another clinical condition that is already listed as an AE. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any SAE that, at any dose:

1. Results in death

2. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect

6. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to ICON Pharmacovigilance and Safety Services and the Sponsor in lieu of completion of the Safety Report Form.

AE and SAE Recording

- There may be instances when copies of medical records for certain cases are requested by ICON Pharmacovigilance and Safety Services and the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to ICON Pharmacovigilance and Safety Services and the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. Symptoms do not require treatment or medical evaluation; signs and symptoms are transient.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities and generally requires systemic drug therapy or other treatment; the event may be incapacitating. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator will assess the causal relationship between study drug and each AE and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the study drug?"
    - No = Unrelated (there is not a reasonable possibility that the study drug caused the event)
    - Yes = Related (there is a reasonable possibility that the study drug caused the event)
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

Assessment of Causality
• There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to ICON Pharmacovigilance and Safety Services and the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to ICON Pharmacovigilance and Safety Services and the Sponsor. • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ICON Pharmacovigilance and Safety Services and the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

10.3.4. Reporting of SAEs

SAE Reporting via Email
• Email transmission of the Safety Report Form is the preferred method to transmit this information to ICON Pharmacovigilance and Safety Services and the Sponsor. • The secondary method for reporting SAEs is notification by fax. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in Table 2.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Person of Childbearing Potential: premenopausal individuals assigned as females at birth who are anatomically and physiologically capable of becoming pregnant following menarche.

Person of Nonchildbearing Potential:

Surgically sterile: individuals assigned as females at birth who are permanently sterile via hysterectomy, bilateral salpingectomy, other procedures that result in the inability to conceive. and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to screening.

Postmenopausal: individuals assigned as females at birth at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory FSH levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, selective estrogen receptor modulators, or chemotherapy. Females on hormone-replacement therapy with FSH levels <40 mIU/mL may be included at the discretion of the Investigator. Females aged >60 years old whose FSH values are not ≥40 mIU/L may be included at the discretion of the Investigator and in consultation with the Sponsor.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy or vasectomy.

10.4.2. Contraception Guidance

Female Participants

Female participants who are persons of nonchildbearing potential will not be required to use contraception. For female participants and other participants assigned as female at birth who are of childbearing potential, an acceptable method of birth control is required from the time of signing the ICF until 90 days after the last dose. Acceptable methods of contraception include:

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion/ligation
- Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (as prescribed)
    1. oral
    2. intravaginal

3. transdermal
4. injectable

- Progestogen-only hormone contraception associated with inhibition of ovulation (as prescribed)
  5. oral
  6. injectable
- Azoospermic partner (vasectomized or due to a medical cause)
  7. Partner must be the sole sexual partner of the woman of childbearing potential and the absence of sperm must have been confirmed. If not, an additional highly effective method of contraception should be used.

Transgender men and non-binary individuals undergoing testosterone therapy may experience amenorrhea (absence of menstruation) and significantly reduced fertility. However, it's important to note that testosterone therapy is not considered a reliable form of contraception for POCBP.

Female POCBP should refrain from donation of ova from check-in (Day -1) until 90 days after the last dose.

Male Participants

Male participants in conjunction with partners of childbearing potential must use the following contraceptive measure:

- condom (even if participant has a history of vasectomy).

For male participants (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the last dose. Male participants are required to refrain from donation of sperm from check in until 90 days after the last dose.

For male participants who were assigned as female at birth, the contraceptive measure of condom use does not apply.

Sexual Abstinence and Same-sex Relationships

A participant who practices total abstinence is required to identify contraceptive methods he/she will use in the event of sexual activity. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

For participants who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a participant who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

10.5. Appendix 5: Toxicity Grading Scales

Table 4: Toxicity Grading Scales for Vital Signs[a]

Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C)	38.0 – <38.5	38.5 – 38.9	≥39.0
Tachycardia - beats per minute	101 – 115	116 – 130	>130
Bradycardia[b] – beats per minute	50 – 54	45 – 49	<45
Hypertension (systolic) - mm Hg[c]	141-150	151-160	≥160
Hypertension (diastolic) - mm Hg[c]	91-95	96-100	>100
Hypotension	85 – 89	80 – 84	<80
Tachypnea – breaths per minute	21-25	26-30	>30

Abbreviations: AE = adverse event; CDISC = Clinical Data Interchange Standards Consortium; FDA = Food and Drug Administration; PI = Principal Investigator

[a] Only changes in vital signs not judged to be related to a stable, comorbid medical condition or consistent with the participant's medical history are to be graded as adverse events based on the above criteria.

[b] These criteria should only be applied when predose heart rates (Screening, check-in, baseline) are between 60 – 100 beats per minute. When predose heart rate is <60 beats per minute, use clinical judgment when characterizing bradycardia in healthy participant populations, for example, conditioned athletes and the timing of the heart rate assessment (eg, during sleep). Out of normal range measurements can be repeated (eg, after participant is awakened). The PI will discuss the case with the Sponsor Medical Monitor before halting the participant's dosing.

[c] Blood pressure grading criteria are based on criteria established for healthy volunteer trials with more restrictive entry criteria. In the population being enrolled in this study, inclusion values for blood pressure overlap with grading criteria. Therefore, clinical correlation to baseline and medical events (eg, blood pressure medications stopped) will be required to assign a grade. Minimally, a confirmed systolic blood pressure >180 mm Hg that represents at least a 20 mm Hg change from baseline, or a confirmed diastolic blood pressure >110 mm Hg that represents at least a 10 mm Hg change from baseline is to be graded as grade 3.

Toxicity grading criteria adapted from FDA Guidance (2007; "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"), to exclude Grade 4 AEs consistent with CDISC reporting requirements.

Table 5: Toxicity Grading Scale for Adverse Events

Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Cardiovascular			
Arrhythmia	Asymptomatic, intervention not indicated	No urgent medical intervention required	urgent intervention indicated
Cardiac ischemia or infarction		Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction
Heart failure	Asymptomatic with laboratory (eg, BNP) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms
Thrombosis or embolism			Urgent intervention indicated
Respiratory			
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms; medical intervention indicated; limiting instrumental activities of daily life	Severe symptoms; limiting self care and interferes with daily activities
Bronchospasm, Acute	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental activities of daily life	Limiting self care activities of daily life; supplemental oxygen indicated
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental activities of daily life	Shortness of breath at rest; limiting self care activities of daily life
GI			
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated
Diarrhea	Increase of <4 stools per day over baseline;	Increase of 4 - 6 stools per day over baseline; limiting instrumental activities of daily life	Increase of >=7 stools per day over baseline; hospitalization indicated; limiting self-care activities of daily life
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated

Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Nervous System Disorders			
Headache	Mild pain	Moderate pain; limiting instrumental activities of daily life	Severe pain; limiting self-care activities of daily life
Other			
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity but not requiring medical intervention	Prevents daily activity and requires medical intervention

Abbreviations: BNP = B-natriuretic peptide; ECG = electrocardiogram; GI = gastrointestinal; IV = intravenous; TPN = total parenteral nutrition.
Toxicity grading criteria adapted from the Common Terminology Criteria for Adverse Events v. 5.0

Table 6: Laboratory Adverse Event Grading Criteria Range Factors

Laboratory Adverse Events[a]	Mild	Moderate	Severe
Parameter	**(Grade 1)**	**(Grade 2)**	**(Grade 3)**
Biochemistry			
ALT	>ULN - 3.0 × ULN if baseline was normal; 1.5 - 3.0 × baseline if baseline was abnormal	>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal	>5.0 × ULN if baseline was normal; >5.0 × baseline if baseline was abnormal
Albumin (hypoalbuminemia)	<LLN - 0.86 × LLN	<0.86 × LLN - 0.57 × LLN	<0.57 × LLN
Alkaline phosphatase	>ULN - 2.5 × ULN if baseline was normal; 2.0 - 2.5 × baseline if baseline was abnormal	>2.5 - 5.0 × ULN if baseline was normal; >2.5 - 5.0 × baseline if baseline was abnormal	>5.0 × ULN if baseline was normal; >5.0 ×baseline if baseline was abnormal
AST	>ULN - 3.0 × ULN if baseline was normal 1.5 - 3.0 × baseline if baseline was abnormal	>3.0 - 5.0 × ULN if baseline was normal >3.0 - 5.0 × baseline if baseline was abnormal	>5.0 × ULN if baseline was normal >5.0 × baseline if baseline was abnormal
Blood bilirubin increased	>ULN – 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 × ULN
Creatinine – mg/dL	>ULN – 1.5 × ULN if baseline was normal; >1.12 baseline - 1.5× baseline if baseline >ULN	>1.5 × ULN – 3.0 × ULN if baseline was normal; >1.5 - 3.0 × baseline if baseline >ULN	>3.0 × ULN if baseline was normal; >3.0 × baseline if baseline >ULN
Glucose (hypoglycemia)	LLN - 0.73 × LLN	<0.73 × LLN – 0.53 × LLN	<0.53 × LLN
Hematology			
Hemoglobin - gm/dL	<LLN - 0.83 × LLN if baseline was normal;	<0.83 × LLN – 0.67 × LLN if baseline was normal;	Hgb <0.67 × LLN if baseline was normal;

Laboratory Adverse Events[a]	Mild	Moderate	Severe
Parameter	**(Grade 1)**	**(Grade 2)**	**(Grade 3)**
	0.83 × baseline, if baseline <LLN	0.83 × baseline – 0.67 × baseline, if baseline <LLN	<0.67 × baseline, if baseline <LLN
WBC Increase - cell/mm^3	>ULN – 1.36 ULN	1.37 × ULN – 1.82 × ULN	>1.82 × ULN
WBC Decrease - cell/mm^3	LLN - 0.67 × LLN	<0.67 × LLN – 0.44 × LLN	<0.44 × LLN
Neutrophils Decrease - cell/mm^3	<LLN - 0.83 × LLN	<0.83 × LLN – 0.56 × LLN	<0.56 × LLN
Platelets Decreased - cell/mm^3	<LLN - 0.5 × LLN	<0.5 × LLN – 0.33 × LLN	<0.33 × LLN
Coagulation			
aPTT	>ULN - 1.5 × ULN	>1.5 - 2.5 × ULN	>2.5 × ULN
INR	>1.2 - 1.5	>1.5 - 2.5	>2.5
Urinalysis			
Protein (if specific gravity >1.015)	1+	2+	>2+
Renal tubular (epithelial) casts/cells	NA	NA	Abnormal

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; Hgb = hemoglobin; INR = International normalized ratio; LLN = lower limit of normal; NA = not applicable; ULN = upper limit of normal; WBC = white blood cells

[a] Factors are applied to LLN or ULN normal range values as dictated by the specified parameter to determine range. Toxicity grading criteria adapted from the Common Terminology Criteria for Adverse Events v. 5.0

10.6. Appendix 6: Abbreviations and Definitions

Abbreviation	Definition
%GCV	percent geometric coefficient of variation
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{0-12}	area under the concentration-time curve from time zero to 12 hours
AUC_{0-t}	area under the concentration-time curve from time zero to last observed concentration at time t
BAL	Bronchoalveolar lavage
BMI	body mass index
CFR	Code of Federal Regulation
CL/F	clearance/bioavailability
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSR	clinical study report
DMID	Division of Microbiology and Infectious Diseases
ECG	electrocardiogram
eCRF	electronic case report form
ELF	Epithelial lining fluid
FEV1	Forced expiratory volume in 1 second
FDA	Food and Drug Administration
FSH	follicle stimulating hormone

Abbreviation	Definition
GCP	Good Clinical Practice
HLT	High level term
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	institutional review board
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PI	Principal Investigator or Package Insert
PK	pharmacokinetic(s)
POCBP	Person of childbearing potential
PT	preferred term
q12h	every 12 hours
QTcF	QT interval corrected for heart rate using Fridericia's method
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Assessments
SOC	system organ class
SOP	standard operating procedure
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event

Abbreviation	**Definition**
T_{max}	time of the maximum observed plasma concentration
UTI	urinary tract infection
V_{ss}/F	Apparent volume of distribution at steady state/bioavailability

10.7. Appendix 7: Bowel Movement Diary

Protocol: VNRX-7145-105
Bowel Movement Diary
Participant Number:_____

Instructions:

Please fill in the details for each bowel movement on a separate row. Bring the completed diary to your Follow-up visit and provide it to the clinic staff.

Date	**Time**	**Bowel Movement Consistency**		
		Normal (formed stools, smooth and/or soft and easy to pass)	Hard (stools that are hard, larger or lumpy and/or defecation straining)	Loose (stools that are mushy or liquid or a mixture of both)
		□ Normal	□ Hard	□ Loose
		□ Normal	□ Hard	□ Loose
		□ Normal	□ Hard	□ Loose
		□ Normal	□ Hard	□ Loose
		□ Normal	□ Hard	□ Loose
		□ Normal	□ Hard	□ Loose
		□ Normal	□ Hard	□ Loose
		□ Normal	□ Hard	□ Loose
		□ Normal	□ Hard	□ Loose

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