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Statistical Analysis Plan

Sponsor:	Venatorx Pharmaceuticals, Inc.
Protocol Identifier:	VNRX-7145-105 (DMID 23-0033)
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
ICON Project Identifier:	VNRX21734 - 21734X 9999/2757
SAP Version Date:	03-Apr-2025

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of ICON Biostatistician/Title:	[redacted] • IEB - Biostatistics
Signature of ICON Biostatistician /Date:	[redacted]
Name of Sponsor Representative /Title:	[redacted]
Signature of Sponsor Representative /Date:	

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3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Venatorx Pharmaceuticals, Inc. Protocol VNRX-7145-105.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 25-Sep-2024 (including all amendments up to this protocol date) and the eCRF version 3.0.

The SAP is expected to be signed and approved before database lock.

This SAP only addresses the results that will be covered by the ICON Early Clinic and Bioanalytical (IEB) Biostatistics Department.

ICON IEB will perform analysis related to the pharmacokinetic (PK) and safety and tolerability objectives.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified in this SAP. Any post hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not necessarily require an updated SAP but should be documented in the Statistical Methods Document and included in the CSR if significant. The ICON statistician will advise when a SAP update is required based on ICON process.

4.0 Changes to Analysis

4.1 Changes from Protocol

There are no changes from the protocol.

4.2 Changes from Previous Version of Approved Statistical Analysis Plan

This is the first version of the SAP.

5.0 Study 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
	  ○ Area under the curve (AUC) from time zero to the last quantifiable sample (AUC0-t)
	  ○ AUC from time zero to 12 hours (AUC0-12)
	  ○ Maximum concentration (Cmax)
	  ○ Terminal-phase half-life (t1/2) in epithelial lining fluid (ELF; if calculable)
	• Plasma PK at steady-state

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Objectives	Endpoints
	○ AUC0-t ○ AUC0-12 ○ Cmax ○ Minimum concentration (Cmin) ○ Time to maximum plasma concentration (Tmax) ○ Clearance/bioavailability (CL/F) ○ Apparent volume of distribution at steady state/bioavailability (Vss/F) ○ t1/2 • Ratios of drug exposure in ELF to plasma using the AUC values for each matrix
Secondary	
To evaluate the safety 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 compared with administration alone.	• Comparison of Group 1 vs Group 2 mean ceftibuten intrapulmonary penetration ratios at 4 hours and 12 hours

6.0 Study 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, approximately 25 participants will each receive a total of 5 doses of ceftibuten-ledaborbactam etzadroxil (CCI [redacted] ceftibuten/CCI [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, 6 participants will each receive a total of 5 doses of CCI [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 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.

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

6.1 Sample Size Considerations

No formal sample size calculation was made. The sample size of 25 evaluable 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 evaluable participants for Group 2 (3 per group at 2 timepoints) is considered sufficient to achieve the secondary objective to the study.

7.0 Randomization and Blinding

This is an open-label, single-sequence study; no randomization or blinding will be conducted.

8.0 Overview of Planned Tables, Figures and Listings Deliveries

8.1 Pre-lock Tables, Figures and Listings

There will be 1 draft run of the tables, figures and listings (TFLs) produced after soft lock and prior to lock. The draft safety TFLs will be provided prior to database lock, with PK concentration listing included if available to assist in the final review of the clinical data, programming and formatting.

As a result of draft TFLs review comments, revisions will be included in the post-lock TFL delivery. Comments affecting the database will be provided to Clinical Data Science.

8.2 Final Analysis

Draft TFLs will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and provided to Sponsor.

9.0 Definitions and General Analysis Methods

9.1 General Data Handling

9.1.1 Rounding

9.1.1.1 Listings

In the listings collected data will be presented with the same precision as the original data as entered in the eCRF or received from external source(s). Derived data will be rounded for presentation purposes.

9.1.1.2 Summary Tables

9.1.1.2.1 General

The following will be rounded regardless of data type

Table 1 Summary General Rounding (Static)

Percentages (including %Coefficient of Variation and % Geometric Coefficient of Variation)	Geometric Mean Ratios and associated Confidence Intervals
1 decimal place	3 decimal places

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The following summary statistics will be rounded relative to the number of decimal places collected.

Table 2 Summary General Rounding (Relative)

Mean/Median	Standard Deviation	Minimum/ Maximum
+1 decimal place	+2 decimal place	+0 decimal places

For collected data, the above rule can be applied directly to the data for summarization.
For derived data the number of decimal places will be determined prior to applying the above rule.
For raw data with inconsistent number of decimals a presentable number of decimals will be used to apply the above rule to (2-3 decimals) at the discretion of the Biostatistician.

9.1.1.2.2 Pharmacokinetic

Pharmacokinetic concentration data is generally recorded to 3 significant figures. Based on this convention the following parameters will have summary statistics presented to the following number of significant figures. If recorded to a different precision these parameters will have the same precision as the data.

Table 3 Summary PK Parameter Rounding

Parameters: All Plasma and ELF PK parameters except Tmax		
Statistic	**Arithmetic Mean, Geometric Mean, Standard Deviation, Minimum, Maximum Median**	**CV%, Geometric CV%**
Precision	3 significant figures	1 decimal place

Pharmacokinetic collected time data is recorded on the eCRF and pharmacokinetic time parameters will be rounded based on collection.

Table 4 Summary PK Time Parameter Rounding

Parameters: T_{max}		
Statistic	**Median**	**Minimum/ Maximum**
Precision	3 decimal places	2 decimal places

Number of observations (n) will always be reported as integers.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Daylight Savings Time Adjustments

On March 09, 2025, at 2:00 am the clocks change to 3:00 am for Daylight Savings Time. The scheduled time of clinic procedures for the remainder of the treatment period will be moved to account for daylight savings time change. All duration calculations (ie, relative time from dosing to PK sample collection and AE duration) that span the time adjustment will need to be programmatically adjusted for the hour that was lost.

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9.1.4 General Descriptive Statistics

Data in tables will utilize the general set of descriptive statistics below. Specific data types may have deviations from the general set of descriptive statistics that will be noted in the sections related to the analysis of that data.

	Continuous Variables						**Categorical Variables**	
Statistic	Number of Observations	Arithmetic Mean	Standard Deviation	Minimum Value	Median Value	Maximum Value	Frequency	Percentage
Term	N	mean	SD	Min	median	max	n	%

For Categorical Data, Percentages by categories will be based on the number of subjects within a group. The categories will be presented exactly as they appear in the electronic case report form (eCRF) / Database. Categories of NOT REPORTED, MISSING, and/or UNKNOWN may be excluded from summaries if null (0).

Unless otherwise noted descriptive statistics will be provided for planned visits from baseline onwards.

Data summarized in tables will have an associated listing. Data listed but not summarized will be noted in specific data type sections.

9.1.5 Pooling

There will be no data pooling across treatments/groups.

9.1.6 Unscheduled Measurements

Unscheduled, repeated and early termination measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled, repeated and early termination measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Common Variable Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline is defined as the last observation recorded before the first study drug administration. The last observation can be an unscheduled / repeated measurement.

9.2.2 Treatment/Subject Grouping

The following Grouping Variables will be used as column headers in the TFL.

Table 5 Treatment Group Definitions

Label	**Grouping**
Study Drug	Ceftibuten, Ledaborbactam Etzadroxil

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Label	Grouping
Treatment	• CTB-LED-E: Ceftibuten Coadministered with Ledaborbactam Etzadroxil • CTB: Ceftibuten Alone
Dose Level	• CTB-LED-E = Ceftibuten (q12h): CCI [redacted] ([redacted] capsules) and Ledaborbactam Etzadroxil (q12h): CCI [redacted] ([redacted] capsules) • CTB = Ceftibuten (q12h): CCI [redacted] ([redacted] capsules)

q12h = every 12 hours

Note: When needing to analyze/display data correctly (eg, baseline), these grouping variables can be assigned to observations both within and outside of the treatment period.

9.2.3 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1 and ADaMIG 1.3.

A define.xml file version 2.1 with the corresponding metadata and Analysis Data Reviewer's Guide (ADRG) produced for data documentation. Analysis Results Metadata (ARM), and analysis displays or program details are excluded from the define.xml.

9.3 Software

The statistical analysis and reporting will be done using SAS® Version 9.4 or higher (SAS Institute, Inc.).

Phoenix® WinNonlin® (WNL) version 8 or higher (Certara, L.P.) will be utilized for noncompartmental analysis (NCA).

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Hypothesis Testing

No formal hypothesis testing will be done. Any P-values or confidence intervals presented should be interpreted in line with the exploratory nature of the study.

9.5 TFL Layout

The layout of TFLs will be according to the ICON Early Phase (IEB) standards.

Table, figure and listing shells are provided with and approved as part of this SAP. Small changes (e.g., footnote removal/addition, columns removed as not relevant, etc.) to shell layout due to the nature of the data may be required after database lock at the discretion of the ICON Biostatistician. Other changes to the shells may be out of scope. The TFLs will be provided as a single document in Adobe PDF format in Letter, and as individual files for each table, figure and listing in Rich Text Format (.rtf).

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10.0 Analysis Sets

The following subject level analysis sets (populations) will be used for summaries in the study.

10.1 Enrolled Population

All participants who signed the informed consent and are enrolled into the study are included in the Enrolled Population.

10.2 Safety Set

The Safety Set will consist of subjects who receive at least one dose of study drug(s). This set will be used for the safety data summaries and baseline characteristic summaries. This set will be analyzed as treated.

10.3 Pharmacokinetic Evaluable Set

The PK Set will consist of all subjects who receive at least one dose of study drug for a profile and have at least one evaluable plasma or BAL concentration. Subjects may be excluded from this set for relevant protocol deviations. This set will be used for the PK concentration summaries and PK parameter summaries. This set will be analyzed as treated.

11.0 Demographic Data

11.1 Subject Disposition

The number and percentage of subjects enrolled, and members of each analysis set will be presented by treatment and overall. The number and percentage of subjects who completed and who discontinued the study prematurely and a breakdown of the corresponding reasons for discontinuation will also be presented.

11.2 Protocol Deviations

Protocol deviations will be collected and reported per ICON's Protocol Deviation Management Standard Operating Procedure (SOP) and relevant Work Instruction (WI). Subject-level deviations will be extracted and pulled into the study tabulation model (SDTM) dataset from ICON's Clinical Trial Management System. Deviations that have been reported and coded as "Important" will be listed by subject. Protocol Deviations will be reviewed prior to database lock and full PK analysis to determine whether any deviations could impact the interpretation of PK data and hence should be excluded from any PK analysis populations.

11.3 Demographics

Subject demographics at screening will be summarized by treatment and overall. The summary will include the subjects' age (years), sex, race, ethnicity, weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Demographics will be summarized for the Safety Set and PK Evaluable Set.

11.4 Medical History

Medical and surgical history, categorized by preferred term according to MedDRA, will be listed by subject.

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11.5 Other Subject Characteristics

Baseline Laboratory measurements including drug screen, alcohol breath test, and pregnancy results will be listed by subject.

Substance use (alcohol, tobacco, and marijuana-containing product) will be listed by subject.

11.6 Concomitant Medications and Procedures

Concomitant medications collected on the eCRF as defined by the protocol will be categorized according to WHO Drug Dictionary. All concomitant medications and procedures will be listed by subject. Medications and procedures with an end date prior to the first dose of study drug will be considered prior and will be noted in the listing. If the end date (eg, partial or missing date) does not confirm a stop prior to first dose the medication or procedure will not be flagged as prior.

11.7 Treatment Compliance and Exposure

The number of subjects receiving each dose of study drug will be summarized. The total dose will be summarized using descriptive statistics. Categorical summaries of study days the dose was taken will be summarized.

12.0 Pharmacokinetic Data

The PK analysis described in the following sections is consistent with Venatorx guidance.

12.1 Pharmacokinetic Variables

Concentrations of ceftibuten, ledaborbactam and urea will be determined in plasma and ELF.

PK parameters of ceftibuten and ledaborbactam will be calculated for plasma and ELF. A full list and definitions of parameters can be found in Appendix 2: Parameter Definitions.

Data on protein binding (fraction bound) of ceftibuten and ledaborbactam will be obtained from other clinical studies or literature and will be used to calculate the free plasma drug concentrations of ceftibuten and ledaborbactam.

12.2 Plasma Pharmacokinetic Summaries

12.2.1 Plasma Concentrations

Plasma concentrations ceftibuten, ledaborbactam, free ceftibuten and free ledaborbactam below the limit of quantification (BLQ) will be as 0 for predose samples and treated as missing for all postdose samples in the computation of descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, SD, coefficient of variation [%CV], percent geometric coefficient of variation (%GCV), median, min, and max) will be used to summarize the plasma concentrations by treatment at each scheduled timepoint.

Linear (+SD) and semi-logarithmic plots of the arithmetic mean plasma concentrations by scheduled sampling time will be provided by treatment. These plots will show time in hours. The plots will present all calculated means and will include a reference line for the lower limit of quantification (LLOQ).

Linear and semi-logarithmic plots of the individual plasma concentrations by actual sampling time will be provided by subject (one subject per page). These plots will show time in hours. Individual plots will use the BLQ handling procedure described below for “Plasma Pharmacokinetic Parameters”.

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Combined semi-logarithmic plots of the individual plasma concentrations by actual sampling time will be provided by treatment group (one treatment per page). These plots will show time in hours. Individual plots will use the BLQ handling procedure described below for "Plasma Pharmacokinetic Parameters".

All individual subject plasma concentration data will be listed by subject. Individual plasma samples that are BQL will be reported as 'BQL' on the data listings or indicated 'BQL' and flagged as a BQL value.

12.2.2 Plasma Pharmacokinetic Parameters

12.2.2.1 Calculation and Summary of PK Parameters

Plasma PK parameters for ceftibuten, ledaborbactam, free ceftibuten, and free ledaborbactam will be estimated by Venatorx and subsequently provided to ICON.

Noncompartmental methods will be used to generate PK parameters for ceftibuten and ledaborbactam in plasma. Maximum plasma concentration (Cmax), time to Cmax (Tmax), and minimum plasma concentration (Cmin) will be obtained from the observed plasma concentration-time profile. The Cmin is defined as the lowest plasma concentration during the 12-hour dosing interval. Area under the plasma concentration-time curve (AUC) at steady state will be computed with the linear-log trapezoidal method and Phoenix WinNonLin (version 8.3, or later, Certara USA, Inc., Princeton, New Jersey). The AUC values will include from time 0 to the time of the last quantifiable concentration (AUC0-last) and from time 0 to 12 hours (AUC0-12). The plasma apparent clearance (CL/F) and apparent volume of distribution at steady-state (Vss/F) will be determined using the standard WinNonLin method. The elimination rate constant (Kel) will be determined by linear regression and the corresponding elimination half-life (t1/2) will be calculated with the equation, t1/2 = 0.693/Kel if sufficient data are available.

Pre-dose plasma concentrations of ceftibuten and ledaborbactam below the limit of quantitation (BLQ) will be treated as zero, and post-dose plasma and ELF concentrations of ceftibuten and ledaborbactam BLQ will be treated as missing values for all pharmacokinetic calculations

Descriptive statistics (n, mean, geometric mean, SD, %CV, %GCV, median, min, and max) will be used to summarize the calculated PK parameters by treatment. For T_{max} only n, median, min and max will be presented.

All parameters will be listed by subject, parameters that meet the exclusion criteria will be accompanied by an indication of criteria met.

12.3 Epithelial Lining Fluid Pharmacokinetic Summaries

12.3.1 ELF Concentrations

The estimations of the ELF volume and drug concentrations in ELF will be calculated with each BAL fluid supernatant from the individual aspirate recovered from the 1st instillation, and pooled aspirate from the 2nd, 3rd, and 4th instillations. The concentration of ceftibuten and ledaborbactam (ABXELF) in the epithelial lining fluid (ELF) will each be determined as follows: ABXELF = ABXBAL x (VBAL / VELF) where ABXBAL is the measured concentration of ceftibuten or ledaborbactam in BAL fluid, VBAL is the volume of aspirated BAL fluid, and VELF is the apparent volume of ELF sampled by the BAL. VELF is derived from the following: VELF = VBAL x UreaBAL / UreaBlood where UreaBAL is the concentration of urea in BAL fluid and UreaBlood is the concentration of urea in blood.

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ELF concentrations ceftibuten and ledaborbactam below the limit of quantification (BLQ) will be treated as missing in the computation of descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, SD, %CV, %GCV, median, min, and max) will be used to summarize the ELF concentrations by treatment at each scheduled timepoint. Each ELF concentration will be corrected for dilution based on ELF/plasma urea concentration ratios.

All individual subject ELF concentration data will be listed by subject.

A separate listing will be provided for Urea concentration measurements.

12.3.2 ELF PK Parameters

Dilution-corrected ELF PK parameters for ceftibuten and ledaborbactam will be estimated by Venatorx and subsequently provided to ICON.

The arithmetic mean concentration values of ceftibuten and ledaborbactam at each BAL sampling time will be calculated and used as a single dataset to estimate the AUC0-12 of plasma and ELF. The elimination rate constant (Kel-ELF) will be determined by linear regression and the elimination half-life (t1/2-ELF) from ELF will be calculated with the equation, t1/2-ELF = 0.693/ Kel-ELF. The AUC0-12 for individual and pooled aspirates of each matrix will be determined with the linear-log trapezoidal method using Phoenix WinNonLin software. The concentration at the 12-hour sampling time also served as a value at time zero for determining the AUC0-12 of plasma and ELF. Drug penetration ratio into ELF (DPRELF/Plasma) will be calculated by dividing the AUC0-12 value for ELF by the AUC0-12 value for unbound plasma. In addition, concentration ratios of ELF to the simultaneous unbound plasma concentration will be calculated for each subject and summarized per group at each sampling time.

All individual subject plasma concentration data will be listed by subject. Individual plasma samples that are BQL will be reported as ‘BQL’ on the data listings or indicated ‘BQL’ and flagged as a BQL value.Descriptive statistics (n, mean, geometric mean, SD, %CV, %GCV, median, min, and max) will be used to summarize the calculated PK parameters by treatment.

All parameters will be listed by subject, parameters that meet the exclusion criteria will be accompanied by an indication of criteria met.

12.4 Statistical Analysis of PK parameters

No formal inferential statistics are planned.

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13.0 Safety Data

13.1 Adverse Events

All AEs as entered on the eCRF (those that started or worsened during the study) will be included in AE listings and summaries (as appropriate).

Treatment emergence will be evaluated for all AEs. Treatment emergent adverse events (TEAEs) are those that occur or worsen after the first dose of study drug.The following missing data will be imputed as defined (for calculations/summary tables only and will not be presented in listings, imputations only for calculations will not be retained in data):

Table 7 AE Data Algorithms

Missing Data Point	Imputation Purpose	Derivation Description
Imputations for calculations only		
Start Time	Calculation of Onset/Duration	Start Time=00:01
End time	Calculation of Onset/Duration	End Time=23:59
Imputations for Displays		
Start Time on dosing day	TEAE determination	TEAE=Y
Start Time on dosing day	Treatment Assignment	Assign AE to treatment given on dosing day
Start Date	TEAE determination	TEAE=Y
Start Date	Treatment Assignment	Assign to treatment given to subject
Severity	Summary Display	Severity=Severe
Relationship	Summary Display	Relationship=Related

A summary of number and percentage of subjects reporting TEAEs, TEAEs by relationship, TEAEs by severity (Toxicity Grading), serious adverse events (SAEs), TEAEs leading to study drug withdrawal, and AEs leading to early termination will be provided by treatment and overall. Total number of TEAE events will also be provided. For the by categories, subjects will be counted under the category of their most related or most severe event in this overall summary. Severity and relationship will be presented as recorded on the eCRF. Relationship will be presented as Related or Not Related. Related will include definitely, probably and possibly related while not related will include unlikely and not related.

A summary of the number and percentage of subjects reporting each TEAE and number of TEAEs, categorized by system organ class (SOC) and preferred term (PT) coded according to the MedDRA, will be presented by treatment and overall. When counting by subject, subjects will only be counted once within each body system or preferred term.

A summary of the number and percentage of subjects reporting each TEAE, categorized by system organ class and preferred term coded according to the MedDRA, will be presented by relationship to study drug (as recorded on the eCRF) by treatment and overall. Subjects with multiple events within a system organ class or preferred term will be counted under the category of their most drug-related event within that system organ class and/or preferred term.

A summary of the number and percentage of subjects reporting each TEAE, categorized by system organ class and preferred term coded according to the MedDRA, will be presented by

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severity (as recorded on eCRF) by treatment and overall. Subjects with multiple events within a system organ class or preferred term will be counted under the category of their most severe event within that system organ class or preferred term.

All AEs (including non–treatment emergent events) recorded on the eCRF will be listed by subject.

A separate listing of AEs where action taken is drug withdrawn will be provided.

13.1.1 Deaths and Serious Adverse Events

A listing of deaths and other SAEs will be provided by subject.

13.2 Clinical Laboratory Data

Clinical laboratory data will be presented as received from the laboratory (no conversion factors applied) using CDISC Synonyms.

In addition to out-of-range flags provided, laboratory results that can be quantitatively graded will be graded for marked abnormalities using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as a guide. The criteria applied and the included laboratory tests are outlined in Appendix 4:

- Biochemistry: ALT; Albumin; Alkaline phosphatase; AST; Blood bilirubin; Creatinine; Glucose;
- Hematology: Hemoglobin; WBC; Neutrophils; Platelets
- Coagulation: aPTT and INR
- Urinalysis: Protein and Renal tubular

The creatinine clearance will be calculated using the Cockcroft-Gault equation:

CL_{CR} = [(140 – age) * body weight] / (baseline serum creatinine (Day -1) *72); multiple by 0.85 if female

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology, and coagulation and changes from baseline by treatment and scheduled time and worst (highest toxicity grade) post-baseline value will be provided only for protocol specified tests. For change calculations pseudo-numeric results (those noted as > or < a number) will be imputed by implementing up or down by one tenth of the smallest unit collected value (e.g. <7 imputed as 6.9 and >7.5 as 7.51).

Urinalysis data will be listed.

All clinical laboratory data will be listed by subject, including laboratory tests not listed in the protocol. A separate listing of out-of-range/abnormal values will also be provided. Normal ranges will be used directly from the clinical laboratory (source data) and will be included in the listings for reference.

Laboratory data will also be summarized using shift tables showing shifts from baseline:

• Low, Normal, and High based on normal ranges as provided directly from the clinical laboratory

• Mild (Grade 1), Moderate (Grade 2), and Severe (Grade 3) (using the marked abnormality flags identified via programming as noted in Appendix 4) will be presented for each post-baseline visit and for worst (highest toxicity grade) post-baseline value.

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13.3 Vital Signs

Graded abnormalities for vital signs will programmatically identified and flagged according to the toxicity grading criteria as presented below and are outlined in Appendix 4:

	Low			Normal	High		
Vital Sign	**Grade 3 (Severe)**	**Grade 2 (Moderate)**	**Grade 1 (Mild)**	**Normal**	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**
Temperature (°C)	N/A	N/A	N/A	35.8 – 37.3	38.0 – <38.5	38.5 – 38.9	≥39.0
Heart Rate (beats/min)	<45	45 – 49	50 – 54	60-100	101 – 115	116 – 130	>130
Systolic Blood Pressure (mm Hg)	<80	80 – 84	85 – 89	90-139	141-150	151-160	≥160
Diastolic Blood Pressure (mm Hg)	N/A	N/A	N/A	60-90	91-95	96-100	>100
Respiration Rate (breaths/min)	N/A	N/A	N/A	12-20	21-25	26-30	>30
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.							

Descriptive statistics summarizing vital signs and changes from baseline by treatment and scheduled time will be provided.

Vital signs will also be summarized using shift tables showing shifts from baseline:

• Low, Normal, and High (using the normal ranges identified via programming as noted above).

• Mild (Grade 1), Moderate (Grade 2), and Severe (Grade 3) (using the abnormal graded flags identified via programming as noted above) will be presented for each post-baseline visit and for worst (highest toxicity grade) post-baseline value for the parameters of temperature increased, heart rate decreased, heart rate increased, systolic blood pressure decreased, systolic blood pressure increased, and respiration rate increased.

All vital signs will be listed by subject, including the programmatically identified high/low flags and graded abnormality flags. A separate listing of abnormal graded vital signs and the worst (highest toxicity grade) post-baseline value will also be provided.

13.4 Electrocardiograms

Descriptive statistics summarizing ECG parameters and changes from baseline by treatment and scheduled time will be provided.

All ECG parameters and the corresponding abnormalities will be listed by subject.

13.5 Bowel Movement Assessments

Descriptive statistics of the number of bowel movements per day after baseline should be presented by treatment.

Bowel movements consistency will also be summarized using shift tables showing shifts from Day - 1:

- Normal, hard, or loose

Each participant should be counted only once per day in the shifting table. If more than one bowel movement is recorded on the same day, the category should be based on the worst observed, with the following order of severity: Loose > Hard > Normal.

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Bowel movement frequency and consistency results will be listed by subject.

13.6 Other Observations Related to Safety

Physical examination results will be listed by subject.

14.0 References

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41. doi:10.1159/000180580.

Clinical Study Protocol. A Phase 1, Open-label Study to Evaluate the Safety and Plasma and Intrapulmonary Pharmacokinetics of Ceftibuten and Ledaborbactam in Healthy Adult Participants. version 2.0, 25-September-2024.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. May 5 2009; 150(9): 604-612.

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. Pharm Res. 2000 Oct; 17(10):1278–83.

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Appendix 1: List of End of Text Outputs

Table 8 List of End of Text Tables and Figures

Output	Title	Analysis Set	Pre-Lock TFL
Section 14.1 – Disposition and Demographic Data			
Table 14.1.1	Summary of Subject Disposition	*Safety*	☒
Table 14.1.2	Summary of Demographics	*Safety*	☒
Table 14.1.3	Summary of study drug Administration	*Safety*	☒
Section 14.2 – Pharmacokinetic Data			
Table 14.2.1.1	Summary of Ceftibuten and Free Ceftibuten Plasma Concentrations	*PK*	☐
Table 14.2.1.2	Summary of Ledaborbactam and Free Ledaborbactam Plasma Concentrations	*PK*	☐
Figure 14.2.2.1	Plot of Mean (+ SD) Ceftibuten and Free Ceftibuten Plasma Concentrations Versus Time	*PK*	☐
Figure 14.2.2.2	Plot of Mean (+ SD) Ledaborbactam and Free Ledaborbactam Plasma Concentrations Versus Time	*PK*	☐
Figure 14.2.3.1	Plot of Individual Ceftibuten and Free Ceftibuten Plasma Concentrations Versus Time on a Linear Scale	*PK*	☐
Figure 14.2.3.2	Plot of Combined Individual Ceftibuten and Free Ceftibuten Plasma Concentrations Versus Time on a Semi–Log Scale	*PK*	☐
Figure 14.2.3.3	Plot of Individual Ledaborbactam and Free Ledaborbactam Plasma Concentrations Versus Time	*PK*	☐
Figure 14.2.3.4	Plot of Combined Individual Ledaborbactam and Free Ledaborbactam Plasma Concentrations Versus Time on a Semi–Log Scale	*PK*	☐
Table 14.2.4.1	Summary of Ceftibuten and Free Ceftibuten Plasma Pharmacokinetic Parameters	*PK*	☐
Table 14.2.4.2	Summary of Ledaborbactam and Free Ledaborbactam Plasma Pharmacokinetic Parameters	*PK*	☐
Table 14.2.5.1	Summary of Ceftibuten Estimated Epithelial Lining Fluid Concentrations	*PK*	☐
Table 14.2.5.2	Summary of Ledaborbactam Estimated Epithelial Lining Fluid Concentrations	*PK*	☐
Figure 14.2.6.1	Plot of Mean (+ SD) Ceftibuten Estimated Epithelial Lining Fluid Concentrations Versus Time	*PK*	☐
Figure 14.2.6.2	Plot of Mean (+ SD) Ledaborbactam Estimated Epithelial Lining Fluid Concentrations Versus Time	*PK*	☐
Table 14.2.7.1	Summary of Ceftibuten Epithelial Lining Fluid Pharmacokinetic Parameters	PK	☐

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Table 14.2.7.2	Summary of Ledaborbactam Epithelial Lining Fluid Pharmacokinetic Parameters	*PK*	☐
Table 14.3.1.1	Overall Summary of Adverse Events	*Safety*	☒
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	*Safety*	☒
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by Relationship to Study Drug	*Safety*	☒
Table 14.3.1.4	Summary of Treatment Emergent Adverse Events by Toxicity	*Safety*	☒
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	*Not applicable*	☒
Table 14.3.3	Not part of TFL – Reserved for Narratives in CSR	*Not applicable*	*NA*
Table 14.3.4	Listing of Abnormal Clinical Laboratory Values	*Not applicable*	☒
Table 14.3.5.1	Summary of Clinical Laboratory Results – Chemistry	*Safety*	☒
Table 14.3.5.2	Summary of Clinical Laboratory Results – Hematology	*Safety*	☒
Table 14.3.5.3	Summary of Clinical Laboratory Results – Coagulation	*Safety*	☒
Table 14.3.5.4	Shift from Baseline in Clinical Laboratory Results Based on Reference Ranges	*Safety*	☒
Table 14.3.5.5	Shift from Baseline in Clinical Laboratory Results Based on Abnormality Grades	*Safety*	☒
Table 14.3.6.1	Summary of Vital Signs Results	*Safety*	☒
Table 14.3.6.2	Shift from Baseline in Vital Signs Based on Abnormality High/Low Determination	*Safety*	☒
Table 14.3.6.3	Shift from Baseline in Vital Signs Based on Abnormality Grades	*Safety*	☒
Table 14.3.7.1	Summary of 12-Lead Electrocardiogram Results	*Safety*	☒
Table 14.3.7.2	Summary of 12-Lead Electrocardiogram Interpretation	*Safety*	☒
Table 14.3.8.1	Summary of Daily Occurrence of Bowel Movement	*Safety*	☒
Table 14.3.8.2	Shift from Baseline in Bowel Movement Consistency	*Safety*	☒

Table 5 List of End of Text Listings

Output	**Title**	**Pre-Lock TFL**
Listing 16.2.1	Subject Disposition	☒
Listing 16.2.2	Important Protocol Deviations	☒
Listing 16.2.3	Analysis Sets	☒
Listing 16.2.4.1	Subject Demographics	☒
Listing 16.2.4.2	Medical History	☒

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Listing 16.2.4.3	Prior and Concomitant Medications	☒
Listing 16.2.5	Study Drug Administration	☒
Listing 16.2.6.1.1	Ceftibuten and Free Ceftibuten Plasma Concentrations	☒
Listing 16.2.6.1.2	Ledaborbactam and Free Ledaborbactam Plasma Concentrations	☒
Listing 16.2.6.2.1	Ceftibuten and Free Ceftibuten Plasma Pharmacokinetic Parameters	☐
Listing 16.2.6.2.2	Ledaborbactam and Free Ledaborbactam Plasma Pharmacokinetic Parameters	☐
Listing 16.2.6.3.1	Ceftibuten Estimated Epithelial Lining Fluid Concentrations	☒
Listing 16.2.6.3.2	Ledaborbactam Estimated Epithelial Lining Fluid Concentrations	☒
Listing 16.2.6.3.3	Urea Blood and Bronchoalveolar Lavage Concentrations	☒
Listing 16.2.6.4.1	Ceftibuten Epithelial Lining Fluid Pharmacokinetic Parameters	☐
Listing 16.2.6.4.2	Ledaborbactam Epithelial Lining Fluid Pharmacokinetic Parameters	☐
Listing 16.2.7.1	Adverse Events	☒
Listing 16.2.7.2	Adverse Events Leading to Study Drug Withdrawal	☒
Listing 16.2.8.1	Clinical Laboratory Results – Chemistry	☒
Listing 16.2.8.2	Clinical Laboratory Results – Hematology	☒
Listing 16.2.8.3	Clinical Laboratory Results – Coagulation	☒
Listing 16.2.8.4	Clinical Laboratory Results – Urinalysis	☒
Listing 16.2.8.5	Clinical Laboratory Results – Drug and Alcohol Screen	☒
Listing 16.2.8.6	Clinical Laboratory Results – Spirometry (FEV1)	☒
Listing 16.2.8.7	Clinical Laboratory Results – Pregnancy Test	☒
Listing 16.2.8.8	Clinical Laboratory Results – FSH	☒
Listing 16.2.8.9	Clinical Laboratory Results – Additional Assessments	☒
Listing 16.2.9.1	Vital Signs	☒
Listing 16.2.9.2	12-Lead Electrocardiogram Results	☒
Listing 16.2.9.3	Bowel Movement Assessments	☒
Listing 16.2.9.4	Physical Examinations	☒

Shells are provided in VNRX-7145-105 Shells 26-Mar-2025 to support the approved SAP.

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Appendix 2: Pharmacokinetic Parameter Definitions

Table 9 Plasma Parameters

Protocol Parameter Presentation*	Dataset Parameter Presentation	TFL Parameter Presentation	(Dataset) Parameter Name	Applicable Analytes for Parameter
C_{min}	Cmin	Cmin	Min Conc	Ceftibuten, Ledaborbactam, free Ceftibuten, and free Ledaborbactam
C_{max}	CMAX	Cmax	Max Conc	Ceftibuten, Ledaborbactam, free Ceftibuten, and free Ledaborbactam
t_{max}	TMAX	Tmax	Time of CMAX	Ceftibuten, Ledaborbactam, free Ceftibuten, and free Ledaborbactam
AUC_{0-t}	AUCLST	AUClast	AUC to Last Nonzero Conc	Ceftibuten, Ledaborbactam, free Ceftibuten, and free Ledaborbactam
AUC_{0-12}	AUCINT + PPSTINT/PPENINT= T1/T2	AUC0-12	AUC from zero to 12 hours	Ceftibuten, Ledaborbactam, free Ceftibuten, and free Ledaborbactam
$t_{1/2}$	LAMZHL	T-HALF	Half-Life Lambda z	Ceftibuten, Ledaborbactam, free Ceftibuten, and free Ledaborbactam
CL	CLO	CL	Total CL Obs	Ceftibuten and Ledaborbactam
CL/F	CLFO	CL/F	Total CL Obs by F	Ceftibuten and Ledaborbactam
CL_{ss}	CLTAU	CLss	Total CL for Dose Int	Ceftibuten and Ledaborbactam
CL_{ss}/F	CLFTAU	CLss/F	Total CL by F for Dose Int	Ceftibuten and Ledaborbactam
V_{ss}	VZTAU	Vss	Vz for Dose Int	Ceftibuten and Ledaborbactam
V_{ss}/F	VZFTAU	Vss/F	Vz for Dose Int by F	Ceftibuten and Ledaborbactam

*Note: Only present for parameter names specified in protocol.

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Table 10 ELF Parameters

Protocol Parameter Presentation*	Dataset Parameter Presentation	TFL Parameter Presentation	(Dataset) Parameter Name	Analyte
AUC0-t	AUCLST	AUClast	AUC to Last Nonzero Conc	Ceftibuten and Ledaborbactam
AUC0-12	AUCINT + PPSTINT/PPENINT= T1/T2	AUC0-12	AUC from zero to 12 hours	Ceftibuten and Ledaborbactam
Cmax	CMAX	Cmax	Max Conc	Ceftibuten and Ledaborbactam
t1/2	LAMZHL	T-HALF	Half-Life Lambda z	Ceftibuten and Ledaborbactam
DPRELF /Plasma	DPRAT	DPRat	Drug penetration ratio in ELF	Ceftibuten and Ledaborbactam
Concentration Ratioxh	CRATXH	CRATxh	Concentration ratio in ELF to free plasma within each subject at the time point(s) where data are available.	Ceftibuten and Ledaborbactam

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Appendix 3: Protocol Schedule of Assessments

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		

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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.

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[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 CCI ceftibuten (CCI capsules) and a dose of CCI ledaborbactam etzadroxil (CCI capsules) will be coadministered orally q12h for a total of 5 doses of each study drug. Group 2 participants will receive a CCI dose of ceftibuten (CCI 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.

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Appendix 4: Toxicity Grading Scales

Table 11 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.

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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 12 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

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Laboratory Adverse Events[a]	Mild	Moderate	Severe
Parameter	**(Grade 1)**	**(Grade 2)**	**(Grade 3)**
Hematology			
Hemoglobin - gm/dL	<LLN - 0.83 × LLN if baseline was normal; 0.83 × baseline, if baseline <LLN	<0.83 × LLN – 0.67 × LLN if baseline was normal; 0.83 × baseline – 0.67 × baseline, if baseline <LLN	Hgb <0.67 × LLN if baseline was normal; <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

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15.0 Version History

Version Date	Modified by	Brief Summary of Changes	Sent to Reviewers
03-Apr-2025	[redacted]	Initial creation from IEB template.	[redacted]

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Certificate Of Completion

Envelope Id: [redacted]
Status: Completed
Subject: VNRX - 7145 -105 | VNRX 21734 - 21734X | SAP Final Signature
Source Envelope:
Document Pages: 29
Signatures: 2
Certificate Pages: 3
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Envelope Originator:
[redacted]
South County Business Park
Leopardstown
Dublin 18, Dublin D18 X5R3
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
03-Apr-2025 | 16:13

Holder: [redacted]
[redacted]

Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Uploaded Signature Image Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 03-Apr-2025 | 16:22 Viewed: 03-Apr-2025 | 18:11 Signed: 04-Apr-2025 | 18:52
Electronic Record and Signature Disclosure: Accepted: 03-Apr-2025 | 18:11 ID: [redacted]		
[redacted] [redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: [redacted] Using IP Address: [redacted] With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document as author	Sent: 03-Apr-2025 | 16:22 Viewed: 03-Apr-2025 | 16:22 Signed: 03-Apr-2025 | 16:23
Electronic Record and Signature Disclosure: Accepted: 03-Apr-2025 | 16:22 ID: [redacted]		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp
[redacted] Venatorx Pharmaceuticals, Inc. Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via Docusign	COPIED	Sent: 03-Apr-2025 | 16:22
[redacted] ICON Research Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Not Offered via Docusign	COPIED	Sent: 03-Apr-2025 | 16:22

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	03-Apr-2025 | 16:22
Certified Delivered	Security Checked	03-Apr-2025 | 16:22
Signing Complete	Security Checked	03-Apr-2025 | 16:23
Completed	Security Checked	04-Apr-2025 | 18:52

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

I understand that my electronic signature is equivalent to my handwritten signature and is therefore legally binding. My electronic signature will remain unique to me and, under no circumstances, am I allowed to disclose my password to any individual which may allow unauthorised access to the system. I understand that I am accountable and responsible for all actions associated with my electronic signature.