**Official Title:** A Phase 1, Open-Label, Randomized, Crossover Study to Assess the Safety and Pharmacokinetics Following Single Doses of Oral and Intravenous Xenleta (Lefamulin) in Adult Patients With Cystic Fibrosis

**NCT Number:** NCT05225805

**Applicant/MAH:** Nabriva Therapeutics

**Version Date:** 16 September 2022

# STATISTICAL ANALYSIS PLAN

## STUDY TITLE: A PHASE 1, OPEN-LABEL, RANDOMIZED, CROSSOVER STUDY TO ASSESS THE SAFETY AND PHARMACOKINETICS FOLLOWING SINGLE DOSES OF ORAL AND INTRAVENOUS XENLETA® (LEFAMULIN) IN ADULT PATIENTS WITH CYSTIC FIBROSIS

## PROTOCOL NUMBER: NAB-BC-3781-1014 (VERSION 1.0)

| | |
|---|---|
| SHORT TITLE: | NAB-BC-3781-1014 |
| NCT#: | NCT05225805 |
| COMPOUND #: | BC-3781 |
| CLIENT: | Nabriva Therapeutics |
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| PREPARED BY: | Rho<br>PI<br>[redacted]<br><br>Minor Updates prior to Database lock:<br>EmpiriStat, Inc.<br>PI [redacted] |

# ACKNOWLEDGEMENT AND SIGNATURE SHEET

| **Approved:** | **Approved:** |
|---|---|
| PI PhD<br>PI, Clinical Research and Development<br>Nabriva Therapeutics | PI, PhD<br>Biostatistician (Consultant) |
| Signature and Date | Signature and Date |
| DocuSigned by:<br>PI | PI<br>PI |

# VERSION HISTORY

| SAP Version | Version Date | Change(s) | Rationale |
|---|---|---|---|
| 1.0 | 16SEP2022 | Not applicable. | Original version. |
| | | | |

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# LIST OF TABLES

# 1. LIST OF ABBREVIATIONS

**Table 1: List of Abbreviations**

| Abbreviation | Term |
|---|---|
| ADaM | Analysis Data Model |
| AE | adverse event |
| ATC | Anatomical Therapeutic Chemical |
| $AUC_{0\text{-}12hr}$ | area under the drug concentration curve from time zero (0 hour [hr]) to 12 hr |
| $AUC_{0\text{-}24hr}$ | area under the drug concentration curve from time zero (0 hr) to 24 hr |
| $AUC_{0\text{-}last}$ | area under the drug concentration curve from time zero (0 hr) to 24 hr |
| $AUC_{\infty}$ | area under the drug concentration curve from time zero (0 hr) to infinity |
| $AUC_{\%extrap}$ | percentage of AUC due to extrapolation for infinity |
| BLQ | below limit of quantification |
| CF | cystic fibrosis |
| CL | clearance |
| CL/F | total body clearance |
| $C_{max}$ | maximum observed plasma concentration |
| CSR | clinical study report |
| CTMS | clinical trial management system |
| CV | coefficient of variation |
| ECG | electrocardiogram |
| F | oral bioavailability |
| HBsAg | Hepatitis B surface antigen |
| HCVAb | Hepatitis C antibody |
| HIV Ab/HIV p24 Ag | Human immunodeficiency virus |
| hr | hour |
| ICH | International Conference on Harmonisation |
| IR | immediate-release |
| IV | intravenous |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRT | mean residence time |
| NA | not applicable |

| Abbreviation | Term |
|---|---|
| PK | pharmacokinetic |
| PT | preferred term |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SDTM | Study Data Tabulation Model |
| SfAS | safety analysis set |
| SOC | system organ class |
| $t_{1/2}$ | apparent elimination half-life |
| TEAE | treatment-emergent adverse event |
| $t_{lag}$ | finite time taken for a drug to appear in systemic circulation following extravascular administration |
| $t_{max}$ | time to reach maximum plasma concentration |
| Vd | volume of distribution |
| Vd/F | volume of distribution corrected for bioavailability |
| Vss | volume of distribution at steady state |
| WHO | World Health Organization |

# 2. PURPOSE OF THE ANALYSES

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the clinical study report (CSR) for Protocol NAB-BC-3781-1014. This document provides details on study populations, how the variables will be derived, how missing data will be handled and details on statistical methods to be used to analyze the pharmacokinetic (PK), efficacy, and safety data. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR as post hoc. Table, listing, and figure specifications are in separate documents.

The SAP is based on International Conference on Harmonisation (ICH) guidelines E3 and E9 (Statistical Principles for Clinical Trials).

The SAP may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by Nabriva Therapeutics, and placed on file before the clinical database is locked. If differences occur between the analyses described in the SAP and the current protocol, those found in the SAP will assume primacy. Deviations from the final approved SAP will be noted in the CSR.

# 3. PROTOCOL SUMMARY

## 3.1 Study Objectives

Primary: To evaluate the pharmacokinetics (PK) of a 600-mg immediate-release (IR) tablet and 150-mg intravenous (IV) formulation of lefamulin in adult patients with cystic fibrosis (CF).

Secondary: To evaluate the safety and tolerability of lefamulin when administered as single oral or IV doses in adult patients with CF.

Exploratory: To approximate the penetration of lefamulin into sputum in CF patients.

## 3.2 Study Endpoints

Primary: Plasma PK parameters of lefamulin and its main metabolite BC-8041 following 150-mg IV infusion and 600-mg IR tablet in patients with CF.

Secondary: Descriptive summaries of the following:

- Treatment-emergent adverse events (TEAEs)
- Laboratory assessments (chemistry and hematology)
- Vital signs measurements
- Electrocardiogram (ECG) parameters

Exploratory: To evaluate the concentration of lefamulin in sputum following 150-mg IV infusion and 600-mg IR tablet in adult patients with CF.

## 3.3 Overall Study Design and Plan

This will be a single-cohort, open-label, randomized, 2-part, crossover study in patients receiving a single dose of lefamulin at 2 study periods 4 to 7 days apart. Lefamulin will be administered as a 600-mg IR tablet orally in the fasted state and a 150-mg IV infusion in 250 mL citrate buffered saline over 1 hour.

## 3.4 Study Population

Patients ≥ 18 years of age with a confirmed diagnosis of CF receiving standard of care will be enrolled in this study. Prior to any study-related procedures being performed, written informed consent will be obtained from all patients.

## 3.5 Treatment Regimens

Study drug will be administered as follows to all patients after an overnight fast:

- IV Treatment Period: lefamulin 150 mg in 250 mL citrate buffered saline IV infusion over 1 hour
- Oral Treatment Period: lefamulin as a 600-mg IR tablet in the fasted state. The oral treatment will be swallowed whole with 6 to 8 ounces of water at least 1 hour before or 2 hours after a meal.

Total duration of study participation for each patient will be approximately 10 to 13 days (from Screening to Follow-up).

## 3.6 Sample Size Determination

Target enrollment for this study will be 12 patients.

# 4. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form n (%). If a count is zero, no percentage will be shown. To ensure completeness, summaries for categorical and discrete variables will include all categories, even if no subjects had a response for a particular category. Missing data for categorical variables will have a 'Missing' category added at the end and the count will be presented with a percentage. When counts are zero, the zero will be presented without a percentage. Percentages for categorical variables will include the 'Missing' category.
- Continuous variables will be summarized using number of subjects, arithmetic mean, median, standard deviation, minimum, and maximum. In addition, PK summaries may include the coefficient of variation (CV), geometric mean and geometric CV. The arithmetic mean, median, and geometric mean will be rounded and reported to 1 more digit than the precision of the original data. The CV, geometric CV, and standard deviation will be rounded and reported to 2 more digits than the precision of the original data. The minimum and maximum will be rounded and reported to the same level of precision as the original observations. If any values are calculated to have more significant digits, then the value should be rounded so that it is the same level of precision as the original data. The level of precision may be modified on specific displays based on clinical judgement.
- Following SAS default rules, the median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- No preliminary rounding should be performed; rounding should only occur after analysis. To round, consider the digit to right of last significant digit: if < 5 then round down, if >=5 then round up.
- In general, listings will be displayed by subject and time of assessment (e.g., visit, time, and/or event) and will be sorted in the order that columns are displayed, starting with the first column on the left.
- Dates in listings will be displayed as YYYY-MM-DD (e.g., 2022-02-11).
- All analyses will be performed using the SAS System version 9.4 or later.
- Page formatting for all tables, listings and figures will be as follows:
    - Page size = 47
    - Line size = 134
    - Font = Courier
    - Font Size = 9
    - Margin = 1.5 inch top, 1 inch bottom, left and right.

- Displays should span fully from the left to right margin, with the white space distributed evenly.
- Display headers will be formatted as:

```
Protocol: NAB-BC 3781-1014                                    Nabriva Therapeutics
```

- Display footers will be formatted as:

```
Program: ProgramName.sas              DDMMMYYY HH: MM                  Page x of y
```

- Displays will be provided in .RTF and .PDF format. Tables, figures, and listings will be stacked into three separate files and provided in .RTF and .PDF format. If possible, a single stacked file including all displays will be provided in .RTF and .PDF format.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

# 5. ANALYSIS SAMPLES

The following definitions will be used to derive the analysis sets for this study.

- PK analysis set: All subjects who receive any full or partial dose of lefamulin and have an evaluable PK profile (plasma concentrations adequate for the calculation of PK parameters). The PK analysis set will be used for the PK analyses.
- Safety analysis set (SfAS): All subjects who receive any full or partial dose of lefamulin. The SfAS will be used for the analysis of safety data.

SfAS/PK analysis sets will be analyzed by actual treatment received, all screened/randomized subjects by randomized treatment. The SfAS analyses will also include summaries overall. For the disposition, demographic, medical history, and prior medications tabular summaries, subjects will be summarized according to their randomized treatment group sequence and overall. Laboratory plots will be presented by actual treatment group sequence.

For tabular PK and SfAS summaries by treatment group, the denominator for percentages may vary by treatment group. For the PK analyses, the number of subjects in the PK analysis set who received a full or partial dose and had an evaluable PK profile for the treatment being summarized will be used as the denominator. For the SfAS analyses, the number of subjects in the SfAS who received a full or partial dose of the treatment being summarized will be used as the denominator. Percentages for overall summaries in the SfAS analyses will use the number of subjects in the SfAS as the denominator.

Select displays will use all screen failures, all subjects screened, or all subjects randomized as the analysis set.

# 6. STUDY SUBJECTS

## 6.1. Disposition of Subjects

The disposition of all screened subjects will be summarized by randomized treatment group sequence and overall. Subjects who failed screening or who were not enrolled (randomized) will only be included in the overall column. The following disposition information will be summarized:

- The number of subjects screened (signed informed consent). Subjects who re-screen will be counted once.
- The number and percentage of subjects who failed screening and the reasons for failure (Did not meet criteria, Withdrew consent, Lost to follow-up, Other).
- The number and percentage of subjects not randomized and the number and percentage of subjects randomized.
- The number and percentage of subjects in each analysis set (PK, SfAS).
- The number and percentage of subjects who completed the study.
- The number and percentage of subjects who discontinued the study early and the reasons for withdrawal (Adverse event, Death, Lost to follow-up, Pregnancy, Withdrawal by subject, Other).
- The number and percentage of subjects who discontinued the study early for reasons related to COVID-19 (Subject has confirmed COVID-19, Site discretion, Subject discretion, Unknown).
- The number and percentage of subjects who discontinued IV treatment early and the primary reason for discontinuation (Adverse event, Death, Lost to follow-up, Withdrawal by subject, Physician decision, Positive drug/alcohol test, Prolongation of the QTc interval or any arrhythmia, Sponsor decision, Failure to meet eligibility criteria, Other).
- The number and percentage of subjects who discontinued oral treatment early and the primary reason for discontinuation (Adverse event, Death, Lost to follow-up, Withdrawal by subject, Physician decision, Positive drug/alcohol test, Prolongation of the QTc interval or any arrhythmia, Sponsor decision, Failure to meet eligibility criteria, Other)..

Percentages for the number of subjects who failed screening, the reasons for failure, the number of subjects not randomized, and the number of subjects randomized will be based on the number of subjects who signed informed consent. Percentages for reasons for premature withdrawal from study treatment will be based on the number of subjects in the SfAS. Percentages for all other rows will use the number of randomized subjects as the denominator. All rows will be summarized by randomized treatment group sequence and overall.

Subject disposition data for all subjects randomized will also be listed. A separate listing of subjects who failed screening with the reason for screen failure will be provided.

A listing of all subjects affected by the COVID-19 pandemic (discontinued the study early or missed visits for reasons related to COVID-19) will be provided by site and subject for all screened subjects to document how the subject's participation was impacted by COVID-19.

## 6.2. Demographic and Other Baseline Characteristics

Summary descriptive statistics for demographic and other baseline characteristics will be reported for the PK and SfAS analysis sets by randomized treatment group sequence and overall. Percentages will use the number of subjects in each analysis set as the denominator. Characteristics to be summarized include:

- Demographic: age, race, ethnicity, sex, and child bearing potential, if female.
- Virology screening: Hepatitis B virus surface antigen (HBsAg) result, Hepatitis C virus antibody (HCVAb) result, and Human immunodeficiency virus (HIV Ab/HIV p24 Ag) antibody result.
- Vital signs: height, body weight, and body mass index (BMI) at screening. BMI will be computed as $\frac{weight(kg)}{height^2(m^2)}$.

Demographic data will also be listed for all screened subjects. Cystic fibrosis diagnosis will be collected for randomized subjects and reported on the demographics listing. Virology screening data will be listed for all randomized subjects. Additional baseline characteristic data to be listed for all randomized subjects includes:

- Pregnancy test results for women of childbearing potential.
- Follicle stimulating hormone at Screening for women who are ≥ 1 year post-menopausal.
- Drugs and alcohol screen.

## 6.3. Prior and Concomitant Medications

Prior medications will include all medications that started and stopped prior to the day of the first administration of any study drug, IV or oral. Concomitant medications will include all medications that started, or were continuing, during or after the first administration of any study drug, IV or oral. Concomitant medications will be attributed to each treatment period as follows:

Treatment Period 1 Treatment (IV or Oral): Concomitant medications will include all medications that started, or were continuing, during or after the first administration of study drug in treatment period 1 and prior to treatment period 2 study drug administration. For subjects who did not receive treatment period 2 study drug (e.g., due to early study discontinuation), all concomitant medications recorded will be attributed to the treatment received in treatment period 1.

Treatment Period 2 Treatment (IV or Oral): Concomitant medications will include all medications that started, or were continuing, during or after the first administration of study drug in treatment period 2.

Concomitant medications that started, or were continuing during or after treatment period 1, and continued into treatment period 2 will be attributed to both the treatment period 1 and 2 treatments.

Where necessary, imputed dates for defining concomitant medications will be used to attribute concomitant medications to each treatment group.

The number and percentage of subjects using concomitant medications will be tabulated by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) class and preferred term (PT) for all subjects in the SfAS by treatment group (actual treatment received) and overall. If a subject has more than one medication within an anatomic class within a treatment period, the subject will be counted only once in that anatomic class. Similarly, if a subject has more than one medication that codes to the same PT within a treatment period, the subject will be counted only once for that PT. Percentages for each treatment group and overall are described in Section 5. The tabular summary will be sorted in descending order based on the overall frequency.

The number and percentage of subjects using prior medications will be tabulated by ATC class and PT for all subjects in the SfAS by randomized treatment sequence and overall If a subject has more than one medication within an anatomic class, the subject will be counted only once in that anatomic class. Similarly, if a subject has more than one medication that codes to the same PT, the subject will be counted only once for that PT. Percentages for each randomized treatment sequence group overall are described in Section 5. The tabular summary will be sorted in descending order based on the overall frequency.

Prior and concomitant medication data will also be presented in a data listing for all randomized subjects.

## 6.4. Medical History

Medical history events will be classified by system organ class (SOC) and PT, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 25.0). Medical history events will be summarized by SOC and PT by randomized treatment sequence and overall for subjects in the SfAS. The summaries will display the number and percentage of subjects experiencing any medical history event as well as the number and percentage of subjects with at least one medical history event in each SOC and PT.

Medical history data will also be listed for all randomized subjects.

# 7. STUDY OPERATIONS

## 7.1. Protocol Deviations

All protocol deviations will be recorded in Rho's clinical trial management system (CTMS). Prior to unblinding and database lock, the medical and study team will perform a blinded review of the protocol deviations to classify the protocol deviations as major or minor.

Protocol deviations will be attributed to each treatment group as follows:

Treatment Period 1 Treatment (IV or Oral) – All protocol deviations that started on or after treatment period 1 study drug administration and prior to treatment period 2 study drug administration. For subjects who did not receive treatment period 2 study drug (e.g., due to early study discontinuation), all protocol deviations that started on or after treatment period 1 study drug administration will be attributed to the treatment received in treatment period 1.

Treatment Period 2 Treatment (IV or Oral) – All protocol deviations that started on or after the treatment period 2 study drug administration.

All subject-level protocol deviations will be summarized in tabular format by actual treatment group, including overall, and type of deviation for randomized subjects. Protocol deviations that started prior to any study drug administration will be reported in the overall column only. Subject-level protocol deviations will also be reported in listings for randomized subjects. The listings will include the subject ID, actual treatment group, date of the deviation, protocol deviation text, protocol deviation type, and classification of major or minor. Any site-level deviations will also be listed.

## 7.2. Randomization

Subjects will be randomized 1:1 to one of two treatment group sequences (Oral – IV, IV – Oral, respectively. Randomization will be accomplished by using a pre-prepared randomization scheme held by the sponsor, assigning subjects to treatment, sequentially across the study as subjects are enrolled.

## 7.3. Measures of Treatment Compliance

The study drug administration listing is described in Section 9.2.

# 8. ENDPOINT EVALUATION

## 8.1. Overview of Efficacy Analysis Methods

### 8.1.1. Multicenter Studies

Study subjects will be enrolled from multiple study sites in the United States. For all analyses, study data will be analyzed and summarized as a whole, and no formal accommodation for site-to-site variation will be made.

### 8.1.2. Assessment Time Windows

The following study visits are scheduled.

| Visit | Visit Number | Visit Window |
|---|---|---|
| Screening | 1 | Up to Day -30 |
| Day -1 | 2 | Day -1 |
| Period 1 Day 1 | 3 | Day 1 |
| Period 2 Day 1 (Also Period 1 Follow-up) | 4 | Period 1 Day 1 + 4-7 |
| Follow-up (Also Period 2 Follow-up) | 5 | Period 2 Day 1 + 4-7 |

The following Day 1 timepoints for Periods 1 and 2 are scheduled.

| Timepoint | Timepoint Number | Timepoint Window |
|---|---|---|
| Pre-dose | 1 | Pre-dose |
| 0.5 hr Post-dose | 2 | 0.5 hr post dosing ± 5 min |
| 1 hr Post-dose | 3 | 1 hr post dosing ± 5 min |
| 1.5 hrs Post-dose | 4 | 1.5 hr post dosing ± 10 min |
| 2 hrs Post-dose | 5 | 2 hr post dosing ± 10 min |
| 4 hrs Post-dose | 6 | 4 hr post dosing ± 30 min |
| 8 hrs Post-dose | 7 | 8 hr post dosing ± 1 hr |
| 12 hrs Post-dose | 8 | 12 hr post dosing ± 1 hr |
| 24 hrs Post-dose | 9 | 24 hr post dosing ± 1 hr |

Note: All timepoints are relative to post infusion start for both IV and oral treatment administration.

All scheduled visit data, including assessments performed outside of the assessment window will be summarized or graphed according to the planned nominal visits. If the planned nominal visit is missing, the nearest unscheduled or early termination visit within the assessment window will be selected for inclusion in tables and figures and reported as the nominal visit. All data, scheduled, unscheduled, and early termination, will be included in listings.

### 8.1.3. Timing of Analyses

Final CSR analyses will be performed after the study is completed and the clinical database is locked.

### 8.1.4. Multiple Comparisons/Multiplicity

Not applicable since treatment comparisons will not be performed.

## 8.2. Primary Endpoint

Plasma PK of lefamulin and its main metabolite, BC-8041, following 150-mg IV infusion and 600-mg IR tablet in patients with CF.

The following PK parameters in plasma for lefamulin and its metabolite BC-8041 will be estimated when possible and appropriate:

| PK Parameter (unit) | Definition | Oral Dose | | IV Dose | |
|---|---|---|---|---|---|
| | | lefamulin | BC-8041 | lefamulin | BC-8041 |
| $C_{max}$ (mg/L) | maximum observed plasma concentration | Yes | Yes | Yes | Yes |
| $T_{max}$ (hr) | time to reach maximum plasma concentration of lefamulin following drug administration | Yes | Yes | Yes | Yes |
| $AUC_{0\text{-}12hr}$ (mg hr/L) | area under the drug concentration curve from time zero (0 hr) to 12 hr | Yes | Yes | Yes | Yes |
| $AUC_{0\text{-}24hr}$ (mg hr/L) | area under the drug concentration curve from time zero (0 hr) to 24 hr | Yes | Yes | Yes | Yes |
| $AUC_{0\text{-}last}$ (mg hr/L) | area under the drug concentration curve from time zero (0 hr) to 24 hr | Yes | Yes | Yes | Yes |
| $AUC_{\infty}$(mg hr/L) | area under the drug concentration curve from time zero (0 hr) to infinity | Yes | Yes | Yes | Yes |
| $t_{½}$ (hr) | apparent elimination half-life calculated as ln(2)/ $\lambda_z$ | Yes | Yes | Yes | Yes |
| CL (L/hr) | clearance calculated as Dose/ $AUC_{\infty}$ | NA | NA | Yes | NA |
| CL/F (L/hr) | total body clearance for extravascular administration calculated as Dose/ $AUC_{\infty}$ | Yes | NA | NA | NA |
| $T_{lag}$ (hr) | the finite time taken for a drug to appear in systemic circulation following extravascular administration | Yes | Yes | NA | Yes |
| $AUC_{\%extrap}$ (%) | percentage of AUC due to extrapolation for infinity | Yes | Yes | Yes | Yes |
| lambda-z ($\lambda_z$) | Individual estimate of the terminal elimination rate constant, calculated using log-linear regression of the terminal portions of the plasma concentration versus-time curves | Yes | Yes | Yes | Yes |
| Vd (L) | volume of distribution calculated as Dose/($\lambda_z$*$AUC_{\infty}$) | NA | NA | Yes | NA |

| PK Parameter (unit) | Definition | Oral Dose | | IV Dose | |
|---|---|---|---|---|---|
| | | lefamulin | BC-8041 | lefamulin | BC-8041 |
| Vd/F (L) | volume of distribution corrected for bioavailability calculated as Dose/($\lambda_z$*AUC∞) | Yes | NA | NA | NA |
| Vss (L) | volume of distribution at steady state | NA | NA | Yes | NA |
| MRT (hr) | mean residence time | Yes | NA | Yes | NA |
| F (%) | oral bioavailability | Yes | NA | NA | NA |
| Metabolite Ratio | AUC∞ of BC-8041/AUC∞ of lefamulin | NA | Yes | NA | Yes |

NA = Not Applicable.

### 8.2.1. Computation of the Primary Endpoint

Plasma PK parameters for each subject will be estimated for lefamulin and its metabolite BC-8041 over the sampling interval for each period using non-compartmental analysis (WinNonlin).

In all PK parameter derivations, 0 will be substituted for concentrations that are below the limit of quantification (BLQ) of the assay. Samples or intervals that are BLQ, but are between two samples or intervals with detectable concentrations will be excluded from the PK analysis.

$C_{max}$ and $T_{max}$ will be determined by direct inspection of the concentration versus time data by WinNonlin.

AUC calculations will be performed using the linear/log trapezoidal rule. $AUC_{0\text{-}12hr}$ will be calculated between $t_{0hr}$ and $t_{12hr}$. $AUC_{0\text{-}24hr}$ will be calculated between $t_{0hr}$ and $t_{24hr}$. $AUC_{0\text{-}last}$ will be calculated between $t_{0hr}$ and the last measurable concentration. AUC∞ will be calculated between $t_{0hr}$ and infinity. The percentage of AUC∞ due to extrapolation for infinity will be calculated as:

$$((C\_last/(lambda\_z\ )))/(AUC\_\infty\ )$$

where

$$C\_last/(lambda\_z\ ) = (AUC\_\infty - AUC\_last\ )$$

Profiles where >20% of the AUC∞ is extrapolated will be marked and excluded from summary statistics.

The terminal elimination rate constant ($\lambda_z$) will be calculated for all subjects using log-linear regression of the terminal portions of the plasma concentration versus-time curves. A minimum of 3 points, not including $C_{max}$, will be used for the regression analysis to determine $\lambda_z$. The number of data points used in calculating $\lambda_z$ will be selected using the Best Fit method in WinNonlin as the number of data points with the largest adjusted $R^2$ value from regression. Elimination rate estimates with an adjusted $R^2$ value of < 0.8 will be marked and excluded from summary statistics. In cases where $\lambda_z$ is not reported, the values for $t_{½}$, AUC∞, CL, CL/F, Vd, Vd/F or Vss will be considered noncalculable and not reported.

Oral bioavailability, F will be calculated as:

$$F = ((AUC\_oral)/(AUC\_IV\ )) * ((Dose\_IV)/(Dose\_Oral\ )) * 100$$

### 8.2.2. Primary Analysis of the Primary Endpoint

Summary descriptive statistics for the PK parameters for lefamulin and separately for its metabolite BC-8041 will be reported for the PK analysis set by actual treatment group. For BC-8041, $AUC_{\%extrap}$ and $\lambda_z$-related parameters will be estimated but not summarized. No treatment comparisons are planned for the PK parameters.

Box and whisker plots for $C_{max}$, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}last}$, and $AUC\infty$ will be presented by actual treatment group and overlaid with geometric means for subjects in the PK analysis set for lefamulin and separately for its metabolite BC-8041. Additional box and whisker plots for other PK parameters may be presented as needed.

Summary descriptive statistics for plasma concentration for lefamulin (mg/L) and separately for its metabolite BC-8041 (mg/L) will be reported for the PK analysis set by actual treatment group. Arithmetic mean (± arithmetic SD) concentration versus timepoint will be plotted on both the linear and semi-logarithmic scale for lefamulin and separately for its metabolite BC-8041 for subjects in the PK analysis set by actual treatment group. The nominal sample timepoint will be used. Individual concentration data versus timepoint will be plotted on both the linear and semi-logarithmic scale for lefamulin and separately for its metabolite BC-8041 for each subject in the PK analysis set and the actual PK sampling time will be used.

Pharmacokinetic parameter data for lefamulin and its metabolite BC-8041 will be listed for subjects in the PK analysis set. Plasma concentration data for lefamulin and its metabolite BC-8041 will be listed for subjects in the SfAS.

## 8.3. Secondary Endpoints

Descriptive summaries of the following by visit and timepoint for the SfAS by actual treatment group:

- Treatment-emergent adverse events (TEAEs) overall
- Laboratory assessments (chemistry and hematology)
- Vital signs measurements
- Electrocardiogram parameters

## 8.4. Other Endpoints

The exploratory endpoint is to evaluate the concentration of lefamulin in sputum following 150-mg IV infusion and 600-mg IR tablet in adult patients with CF. Summary descriptive statistics for the concentration of lefamulin in sputum will be reported for the SfAS by actual treatment group and timepoint. No treatment comparisons are planned.

## 8.5. Examination of Subgroups

None planned.

# 9. SAFETY EVALUATION

The evaluation of the safety and tolerability of lefamulin when administered as single oral and IV doses in adult patients with CF is the secondary objective of this study. The endpoints described in Section 8.3 are part of the safety evaluation. Descriptive summaries will be performed for the SfAS by actual treatment group and will include TEAEs, serious adverse events (SAEs), laboratory assessments (chemistry and hematology), vital signs, and ECG. Study medication exposure, physical examination, and concomitant medications will also be included as part of the safety evaluation.

## 9.1. Overview of Safety Analysis Methods

For all safety endpoints, baseline will be defined separately for each treatment period as the last non-missing value before the first study drug administration in the treatment period. For laboratory values, baseline values for the second treatment period are scheduled to be collected at the last follow-up assessment for the first treatment period. For vital signs and ECG, baseline values for each treatment period are scheduled to be collected at the Day 1 Pre-dose assessment for each treatment period.

For all change from baseline analyses, change from baseline will be defined as the post-baseline measurement minus the baseline measurement.

For all shift from baseline analyses, percentages will be based on the number of subjects in each category at baseline. A 'Missing' category will be added for subjects missing post-baseline assessments and the count will be presented with a percentage. When counts are zero, the zero will be presented without a percentage.

Safety data will not be imputed, except for partial and missing dates, missing adverse event severity (intensity), and missing adverse event relationship to study drug. Partial and missing dates will be imputed only for defining TEAEs and concomitant medications. Imputed data will not be presented in data listings.

Partial dates will be imputed for the purposes of defining TEAEs and concomitant medications as follows:

- For a missing start day where the month and year are present, the start day will be set to the first day of the month, unless the following two conditions are met:
  1. the first day of the month is before the first date of administration of study drug and the month and year are the same as the month and year of the first date of administration of study drug, and
  2. the end date is on or after the first date of administration of study drug or the end date is completely missing.

  If the two above conditions are met, the start day will be set to the day of administration of study drug.
- For a missing start day and month where the year is present, the start day and month will be set to January 1st, unless 1) January 1st is before the first date of administration of

study drug and the year is the same as the year of the first date of administration of study drug, and 2) the end date is on or after the first date of administration of study drug or the end date is completely missing, in which case the start day and month will be set to that of the first date of administration of study drug.

- For a missing end day where the month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the month and year of the last contact date for the subject, in which case the end day will be set to that of the subject's last contact date.
- For a missing end day and month where the year is present, the end day and month will be set to the subject's last contact date, unless the year of the subject's last contact date is greater than the end year, in which case the end day and month will be set to December 31st.
- For an entirely missing start date (i.e., day, month, and year are missing), the start date will be set to the first date of administration of study drug unless the stop date is prior to the first date of administration of study drug, in which case the start date will be set to the stop date.
- For an entirely missing stop date (i.e., day, month, and year are missing), the AE or medication will be treated as ongoing.

Imputation for adverse events with missing severity (intensity) or relationship to study drug is described in Section 9.3. Imputed values will be reported in summary tables, but will not be presented in listings.

## 9.2. Extent of Exposure

The following exposure data at Day 1 will be summarized by actual treatment group and overall for subjects in the SfAS.

- The number and percentage of subjects who received any treatment.

For the oral treatment group only:

- The number and percentage of subjects who took dose 1 hour before a meal or 2 hours after a meal.

For the IV treatment group only:

- The number and percentage of subjects who received complete IV treatment.
- The number and percentage of subjects with IV administration of study treatment interrupted.
- The duration of IV treatment (minutes), summarized descriptively as a continuous variable.
- The duration of the treatment interruption (minutes), summarized descriptively as a continuous variable.

- The total amount of study treatment administered (mL), summarized descriptively as a continuous variable.

The number and percentage of subjects who received study treatment in a different order than specified in the randomized treatment sequence will also be summarized in the overall column only.

## 9.3. Adverse Events

AEs will be collected throughout the study from the time a subject signs the informed consent through the follow-up assessment after the second dosing period. All AEs will be classified by SOC and PT, according to a standardized thesaurus (Medical Dictionary for Regulatory Activities [MedDRA] version 25.0). The severity (intensity) of AEs will be classified as Mild, Moderate and Severe as defined in Section 9.2 of the protocol. Severity will also be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE). Summary tabulations for AE severity will be based on the protocol definitions and the CTCAE grading will be reported in listings.

AEs with a start date and time on or after the date and time of the first study drug administration will be classified as TEAEs. Events that started before first study drug administration and worsened in severity will also be classified as TEAEs. Only TEAEs will be presented in summary tables by actual treatment group and overall for subjects in the SfAS. All AEs will be listed for subjects in the SfAS with a flag indicating if the AE was treatment-emergent. TEAEs will be attributed to each treatment group as follows:

Treatment Period 1 Treatment (IV or Oral) – All TEAEs that started prior to treatment period 2 study drug administration. For subjects who did not receive treatment period 2 study drug (e.g., due to early study discontinuation), all TEAEs recorded will be attributed to the treatment received in treatment period 1.

Treatment Period 2 Treatment (IV or Oral) – All TEAEs that started on or after the treatment period 2 study drug administration. TEAEs that started during treatment period 1 and continued into treatment period 2 without worsening in severity in treatment period 2 will be attributed to the treatment period 1 treatment.

TEAEs that started during treatment period 1 and continued into treatment period 2 with worsening in severity in treatment period 2would have had a new record created in the EDC with the start date based on when the AE worsened. The record with the start date during treatment period 1 will be attributed to treatment period 1 and the record with the start date during treatment period 2 will be attributed to treatment period 2.

Where necessary, imputed dates for defining TEAEs will be used to attribute TEAEs to each treatment group.

TEAEs will be summarized in an overall table by actual treatment group and overall for subjects in the SfAS and will include:

- Total number of TEAEs

- Total number of TEAEs indicated as serious
- Total number of TEAEs related to study drug
- The number and percentage of subjects with at least one TEAE
- The number and percentage of subjects with at least one serious TEAE
- The number and percentage of subjects with at least one TEAE related to study drug
- The number and percentage of subjects with at least one TEAE leading to study drug discontinuation
- The number and percentage of subjects with at least one TEAE leading to death
- The number and percentage of subjects with TEAE with maximum severity of Mild (only counting the subject in the highest severity)
- The number and percentage of subjects with TEAE with maximum severity of Moderate (only counting the subject in the highest severity)
- The number and percentage of subjects with TEAE with maximum severity of Severe (only counting the subject in the highest severity)
- The number and percentage of subjects with Related TEAE with maximum severity of Mild (only counting the subject in the highest severity)
- The number and percentage of subjects with Related TEAE with maximum severity of Moderate (only counting the subject in the highest severity)
- The number and percentage of subjects with Related TEAE with maximum severity of Severe (only counting the subject in the highest severity)

If a subject experiences the same AE on multiple occasions, the event will be counted once for each occurrence when reporting the number of TEAEs. When reporting the number of subjects experiencing events, a subject will only be counted once. Percentages will be based on the number of subjects in the SfAS by actual treatment group.

TEAEs classified by MedDRA SOC and PT will be summarized by actual treatment group and overall. The summaries will display the number and percentage of subjects experiencing any TEAE as well as the number and percentage of subjects with at least one TEAE in each SOC and PT for each of the following:

- All TEAEs
- Related TEAEs
- All TEAEs leading to study drug discontinuation
- TEAEs by maximum severity (intensity)
- TEAEs by maximum relationship to study drug

If a subject has more than one AE within a SOC, the subject will be counted only once in that SOC. If a subject has more than one AE that codes to the same PT, the subject will be counted only once for that PT. The tabular summaries will be sorted by descending frequency by SOC and PT for the overall incidence.

In the TEAEs by maximum severity and maximum relationship to study drug summaries, severity (intensity) will be rated as Mild, Moderate, or Severe based on the definitions in Protocol Section 9.2 and relationship to study drug will be scored as Definitely Related, Probably Related, Possibly Related or Not Related. In the event that severity (intensity) or relationship data are missing, the study analysis will follow the assumption of maximum relationship or severity in the summary tables. If a subject has more than one AE within a SOC or PT within a treatment period, the subject will be counted only once for that event under the maximum severity or most related category for the study drug. The tabular summaries will be sorted by descending frequency by SOC and PT for the overall incidence.

All AEs will be presented in data listings for all randomized subjects.

## 9.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

TEAEs resulting in death and serious TEAEs will be summarized by SOC and PT for subjects in the SfAS by actual treatment group and overall. Rules for counting TEAEs are the same as those described in Section 9.3.

All TEAEs resulting in death and serious TEAEs will be presented in data listings for all randomized subjects. The listing of TEAEs resulting in death will also report the death date and cause of death.

## 9.5. Clinical Laboratory Evaluation

Clinical laboratory measurements to be summarized for the safety evaluation include the serum chemistry and hematology parameters listed in Protocol Appendix 1. Laboratory normal range data will be collected at each site and stored in the Medidata Lab Administration Module and subsequently mapped to study data tabulation model (SDTM) and analysis data model (ADaM) datasets for use in analysis. Mayo clinic laboratory ranges will be used in the Medidata Lab Administration Module when laboratory normal range data are not available at a site. Mayo clinic laboratory ranges will be mapped to SDTM and ADaM datasets for use in analysis. Numeric laboratory results will be classified as low, normal, or high based on the specific result falling below, within, or above the laboratory normal range, respectively.

For numeric laboratory results, descriptive statistics of laboratory values and the change from baseline of laboratory values at each visit and timepoint will be presented by actual treatment group and overall for subjects in the SfAS. The number and percentage of subjects with laboratory results classified as low, normal, or high will be summarized for each laboratory test by visit and timepoint, actual treatment group and overall for subjects in the SfAS. Shift from baseline tables will also be produced for each laboratory test by visit and timepoint, actual treatment group and overall for subjects in the SfAS.

Numeric laboratory result data will also be plotted by subject over time (Planned timepoints: Screening, Day -1, Period 1 Day 1 24 hrs Post-dose, Period 2 Day 1 24 hrs Post-dose). For each test, data will be plotted as a spaghetti plot where each subject's values will be plotted and connected by line segments, forming one line per subject. The plots will be paginated by actual treatment group sequence within each test.

Serum chemistry and hematology data, including the assessment for clinical significance, will be listed for all randomized subjects.

## 9.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

### 9.6.1. Vital Signs

Descriptive statistics of numeric vital signs results and change from baseline of vital signs at each visit and timepoint will be presented by actual treatment group and overall for subjects in the SfAS. Vital signs results will also be classified as Low, Normal, or High and summarized in shift tables from baseline to each post baseline visit and timepoint by actual treatment group and overall for subjects in the SfAS. The following categories will be used to assess clinical relevance for vital signs data.

| Vital Sign | Low | Normal | High |
|---|---|---|---|
| Systolic Blood Pressure (mmHg) | <90 | 90-160 | >160 |
| Diastolic Blood Pressure (mmHg) | <50 | 50-90 | >90 |
| Heart Rate (beats per minute) | <60 | 60-100 | >100 |
| Respiration Rate (breaths per minute) | <12 | 12-20 | >20 |

Vital signs data will also be listed for all randomized subjects.

### 9.6.2. Physical Examinations

Physical examination data will be listed for all randomized subjects.

### 9.6.3. Other Safety Measures

### 9.6.4. ECG

Descriptive statistics of numeric ECG results and change from baseline of ECG at each visit and timepoint will be presented by actual treatment group and overall for subjects in the SfAS. ECG parameters to be summarized include heart rate, PR interval, QT interval (uncorrected), QTcF – Fridericia's correction formula, QRS duration, and RR interval.

ECG overall interpretation will be summarized in a shift table from baseline to each post baseline visit and timepoint by actual treatment group and overall for subjects in the SfAS.

ECG results will also be also be categorized based on the magnitude of QTcF and the change from baseline. The number and percentage of subjects will be summarized for the following categories:

Absolute QTcF
- ≤450 msec
- >450 and ≤480 msec
- >480 and ≤500 msec
- >500 msec

Post-Infusion change in QTcF
- < 30 msec
- 30 to 60 msec
- > 30 msec
- > 60 msec

Post-Infusion QTcF value >450msec and
- Change >30 msec
- Change >60 msec

Post-Infusion QTcF value >500 msec and
- Change >30 msec
- Change >60 msec

ECG data will also be listed for all randomized subjects.

### 9.6.5. Concomitant medications

Concomitant medication summaries are described in Section 6.3.

# 10. PHARMACOKINETIC EVALUATION

The pharmacokinetic evaluation for this study is specified in Section 8.2 of the SAP.

# 11. OTHER ANALYSES

None.

# 12. INTERIM ANALYSES AND DATA MONITORING

Not applicable.

# 13. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

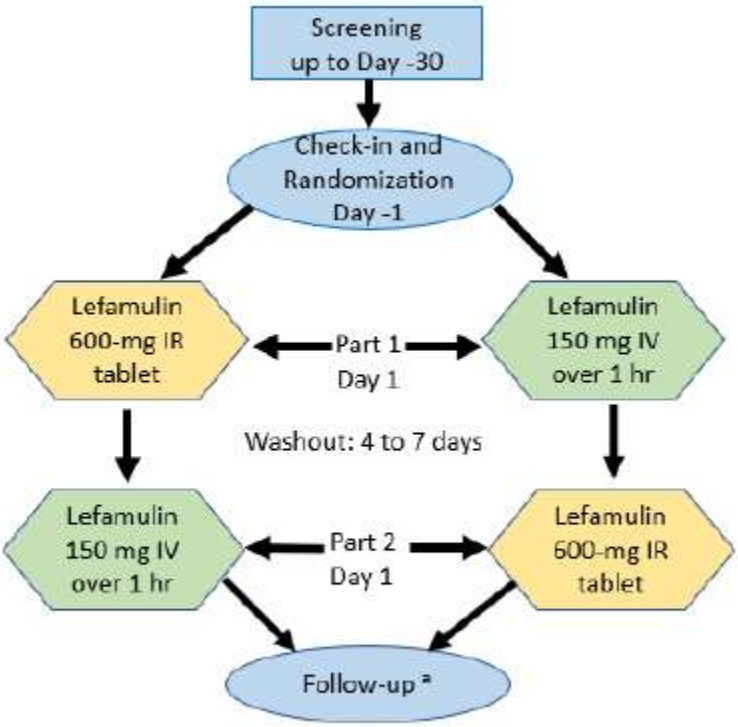
None.

# 14. REFERENCES

None.

# 15. APPENDIX

## 15.1. Study Flow Chart




Abbreviations: hr = hour; IR = immediate-release; IV = intravenous
[a] For the first dosing period, the Follow-up Visit may be used as the Screening Visit for the second dosing period. For the second dosing period, a Follow-up phone call will take place 4 to 7 days post final dose.

## 15.2. Schedule of Events

| | | IV Treatment Period and Oral Treatment Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Day 1 Post-dose | | | | | | | | |
| Study Procedure | Screening[a] | Day -1[b] | Day 1 pre-dose[c] | Day 1 | 0.5 h | 1 h | 1.5 h | 2 h | 4 h | 8 h | 12 h | 24 h | Follow-up[d] |
| Assessment window | D -30 to -1 | – | – | – | ± 5 m | ± 5 m | ± 10 m | ± 10 m | ± 30 m | ± 1 h | ± 1 h | ± 1 h | 4 to 7 days |
| Informed consent | X | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | |
| Medical/medication history | X | X | | | | | | | | | | | |
| Physical examination [e] | X | X | | | | | | | | | | X | |
| Height and weight | X | | | | | | | | | | | | |
| Vital signs[f] | X | | X | | X | | | X | | | | X | |
| 12-lead ECG | X | | X | | X[g] | | | X[h] | | | | | |
| Blood for chemistry, hematology, virology | X[i] | X | | | | | | | | | | X | |
| Drugs and alcohol screen | X | X | | | | | | | | | | | |
| Pregnancy test (serum or urine)[j] | X | X | | | | | | | | | | | |
| Sputum collection[k] | | | X | ◄ | | | | X | | | | ► | |
| Study drug administration[l] | | | | X | | | | | | | | | |
| Plasma for PK | | | X | | X | X | X | X | X | X | X | X | |
| Adverse event monitoring | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Medications | | | X | X | X | X | X | X | X | X | X | X | X |
| Discharge from CRU[m] | | | | | | | | | | | | X | |

Abbreviations: AE = adverse event CRU = clinical study unit; D = study day; ECG = electrocardiogram; h = hour(s); IV = intravenous; m = minute(s); PK = pharmacokinetics

a. Informed consent must be obtained before study specific-procedures are performed. However, assessments performed as part of standard of care within the screening period may be used to determine eligibility.
b. After completion of all Day -1 assessments, patients who remain eligible per entry criteria will be admitted to the CRU. Day -1 assessments do not have to be repeated if Screening occurred within 72 hours.
c. Day 1 pre-dose testing and sample collection should be performed within 2 hours before dosing.
d. A Follow-up phone call will take place 4 to 7 days after the final dose. For any AEs or other issues of concern, investigators, at their discretion, may ask patients to return to the study site for an in-person visit (this would be considered an unscheduled visit).
e. Complete physical examinations will be performed at Screening and Day -1; a focused physical examination will be performed on Day 1 at 24 hours.
f. Systolic blood pressure, diastolic blood pressure, body temperature, heart rate, respiratory rate, oxygen saturation
g. IV Treatment Period only (following IV dosing)
h. Oral Treatment Period only (following oral dosing)
i. Includes viral serology at Screening
j. Follicle stimulating hormone (FSH) level will be determined for women who are ≥ 1 year post-menopausal.
k. Sputum should be collected first thing in the morning on Day 1 pre-dose, then collect as many sputum samples as possible.
l. IV Treatment Period: IV dose infused over 1 hour (± 2 minutes); Oral Treatment Period : the oral treatment will be swallowed whole with 6 to 8 ounces of water at least 1 hour before or 2 hours after a meal.
m. Patient may be discharged from the CRU after completion of all 24-hour procedures and Investigator determination that no additional safety monitoring is required.