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: 02 November 2021

XENLETA® (LEFAMULIN)

NAB-BC-3781-1014

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

US IND 106594

Protocol Status	Version	Date
Original	1.0	02 November 2021

INVESTIGATOR SIGNATURE PAGE

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 NAB-BC-3781-1014

In conducting this clinical study, I agree to be responsible for:

- Ensuring that the clinical investigation is conducted according to the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, October 2013), the Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation (ICH) (CPMP/ICH/135/95), the signed Form Food and Drug Administration (FDA) 1572 Statement of Investigator (applies to all studies conducted under a United States Investigational New Drug Application) and other applicable local and national laws and requirements.
- Protecting the rights, safety, and welfare of patients under my care.
- Maintaining control of the drugs under investigation.

I also agree to conduct the study as detailed in the protocol and in accordance with Nabriva Therapeutics guidelines and all applicable government regulations. These guidelines and regulations include, but are not limited to:

- Permission to allow Nabriva Therapeutics and regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, which ensures patient confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify Nabriva Therapeutics as soon as possible thereafter (no later than 1 week).
- Submission of the proposed clinical investigation, including the protocol, the informed consent documents, and any other patient materials required for study conduct, to a duly constituted Institutional Review Board (IRB) for approval, and acquisition of written approval for each, before the use of the study drug.
- Obtaining written informed consent only after ensuring that the patient, or his/her legal representative, is competent to make the decision, understands what is contained in the informed consent document, and is consenting voluntarily. Written informed consent will be obtained before administration of study drug or any non-routine study-related procedures; the document contains all the essential elements of consent and has been previously approved by the Sponsor and IRB. Reference of written informed consent will be provided in source documentation.
- Submission of any protocol amendment to an accredited IRB. Institutional Review Board written approval must be obtained before implementation of any protocol amendment.
- Adherence to the study protocol. Documentation and explanation of individual post-enrollment protocol deviations will be recorded in the source documentation at the site and be provided to Nabriva Therapeutics.

- Notification to Nabriva Therapeutics of all serious adverse events (SAEs), regardless of relationship to study drug, as specified in the protocol. Notification to the IRB of SAEs as specified in the protocol and as per the guidelines provided by the IRB.
- Notification to the IRB of all unanticipated problems within the timeframe provided by the IRB. For the purposes of this study, unanticipated problems are defined as any incident, experience, or patient outcome that meets **all** of the following criteria: (1) unexpected; (2) related or possibly related to participation in the study; (3) and suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known.
- Provision of adequate study oversight by personally conducting or supervising the investigation, including, but not limited to: allotting sufficient time to properly conduct and complete the study within the agreed upon time period; having available an adequate number of qualified staff and adequate facilities for the expected duration of the study and to conduct the study properly and safely; and ensuring that all persons assisting with the study are adequately informed about the protocol and the investigational product(s) and are capable of performing their study-related duties and functions. Qualifications of individuals assigned responsibility for the administration of the investigational product will be compliant with state and local law or national regulations, as applicable.
- Submission of timely progress reports to the IRB and Nabriva Therapeutics at appropriate intervals not to exceed 1 year and submission of a final report to the IRB within the timeframe set by the IRB, but not later than 3 months after the completion or termination of the clinical investigation.
- Maintenance of accurate source records from which electronic case report forms (eCRFs) are completed as well as drug accountability records that show the receipt and disposition (on an overall and per patient basis) of all study drug(s) shipped to the Investigator by Nabriva Therapeutics.

In addition, I agree to provide all the information requested in the eCRF presented to me by Nabriva Therapeutics by carefully following the completion guidelines provided as part of the eCRF.

If I opt to terminate my participation in the study, the foregoing shall equally apply.

_____

Investigator's Name (Please Print)

_____ _____

Investigator's Signature Date

Sponsor-related Contact Details

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 NAB-BC-3781-1014

Sponsor:	Nabriva Therapeutics Ireland DAC Alexandra House, Office 225/227 The Sweepstakes Ballsbridge Dublin 4 D04 C7H2 Republic of Ireland
Sponsor's Study Manager:	PI , PI , Project and Alliance Management
Sponsor's Medical Officer:	PI , MD, MBA, MPH
Sponsor's Selected CRO:	PI
Pharmacovigilance:	PrimeVigilance
Bioanalytical Laboratory:	PI
Pharmacokinetics and Statistical Analysis	PI

2. SYNOPSIS

Name of Sponsor/Company: Nabriva Therapeutics	
Name of Investigational Product: XENLETA® (lefamulin)	
Name of Active Ingredient: Lefamulin (BC-3781)	
Title of Study: 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	
Number of study centers: Approximately 6	
Principal Investigator: PI [redacted]	
Studied period (years): Estimated date first patient enrolled: Jan 2022 Estimated date last patient completed: Mar 2023	**Phase of development:** 1
Objectives: **Primary:** • To evaluate the pharmacokinetics (PK) of a 600-mg immediate-release (IR) tablet and 150-mg intravenous (IV) formulations 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	
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	

Methodology:

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.

Number of patients (planned):

Approximately 12 patients are planned to be enrolled.

Diagnosis and main criteria for inclusion:

Key inclusion criteria are as follows:

1. Signed informed consent.
2. Adult patients, ≥ 18 years of age.
3. Genetic confirmation of CF diagnosis by a report from a genetic test, such as "F508 deletion detected."
4. Weight > 40 kgs.
5. Forced expiration volume (FEV)1 > 40% predicted, as measured during the most recent evaluation.
6. Mentally and physically able to participate in the study as determined by the Investigator, ie, clinically stable with no significant changes in health status within 28 days prior to, and including, Day 1.
7. Vital signs within the following ranges:
    a. Tympanic temperature, < 38°C
    b. Systolic blood pressure, 90 to 160 mmHg
    c. Diastolic blood pressure, 50 to 90 mmHg
    d. Heart rate < 100 beats per minute at rest
    e. Respiration rate 12 to 20 breaths per minute
    f. Oxygen saturation to be documented. No selection criteria; supplemental oxygen use is acceptable.
8. Negative beta-human chorionic gonadotropin (β-hCG) urine or serum pregnancy test for females of childbearing potential.
9. Willing to commit to acceptable methods of contraception as defined in the protocol.

Key exclusion criteria are as follows:

1. Known history of chronic liver or biliary disease, Gilbert's syndrome, or any of the following at Screening: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x upper limit of normal (ULN), total bilirubin > 1.5 x ULN.
2. Prolonged baseline corrected QT interval corrected according to Fridericia (QTcF) defined as > 440 ms (females) and > 430 ms (males).
3. Family history or presence of prolonged QTc syndrome, Torsades de Pointes, or known conduction defects (eg, bundle branch block, atrioventricular block).
4. Use of Orkambi® (lumacaftor/ivacaftor) within 28 days prior to Day 1.
5. Use of cytochrome P450 (CYP)3A substrates that prolong the QT interval within 24 hours prior to Day 1.

6. Use of strong and moderate CYP3A inducers or P-glycoprotein (P-gp) inducers within 28 days prior to Day 1.
7. Use of strong inhibitors of CYP3A4 within 24 hours prior to Day 1.
8. Serum potassium level below the normal reference range at Screening.
9. Known allergy to pleuromutilin class of antibiotic or any of the excipients of the lefamulin formulations.
10. Consumption of grapefruit, grapefruit juice, grapefruit products, pomelo, or Seville oranges within 24 hours before Day 1.
11. Use of vaporized nicotine or cannabidiol products, smoking (regularly or intermittently) more than 5 cigarettes (or equivalent) per day, or any use of tobacco other than in cigarettes or cigars within 28 days of Day 1.
12. Positive blood test for hepatitis C, human immunodeficiency virus (HIV), or hepatitis B antigen or core antibody (indicating active infection).
13. Positive test for drugs of abuse or alcohol at Screening or Day -1 that cannot be satisfactorily supported by medical history.
14. Use of an investigational product within the 30 days prior to Day 1 (3 months prior to Day 1 if the study drug was a new chemical entity).
15. Difficulty swallowing tablets.
16. Females who are pregnant or breastfeeding.
17. Does not have suitable venous access for multiple venipuncture or cannulation.
18. Any medical, psychological, cognitive, social, or legal conditions that, in the opinion of the Investigator, would interfere with the patient's ability to give an informed consent and/or participate fully in the study.
19. Any other reason, in the opinion of the Investigator, the patient is unsuitable to participate.

Investigational product, dosage, and mode of administration:

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.

Duration of treatment:

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

Reference therapy, dosage, and mode of administration:

None

Criteria for evaluation:

Pharmacokinetics:

Blood samples will be taken for the measurement of PK parameters at the following time points in each part of the study:

- Pre-dose; 30 min, and 1, 1.5, 2, 4, 8, 12, and 24 hours post-dose.

Sputum samples will be collected first thing in the morning on Day 1 (pre-dose), and spontaneous sputum samples may be collected through 24 hours post-dosing as often as the patient can provide a sample. The exact time of the sputum collection will be documented for determination of PK parameters of lefamulin in sputum.

Safety:

Safety will be evaluated with the following assessments:

- Adverse events and concomitant medications will be monitored and recorded throughout the study.
- Clinical chemistry and hematology assessments will be performed at Screening, Day -1, and 24 hours post-dose; laboratory assessments will be conducted at Follow-up only if necessary.
- Vital signs will be measured at Screening, pre-dose on Day 1, at 0.5 hours, 2 hours, and 24 hours post-dose; vital signs will be measured at Follow-up only if necessary.
- Electrocardiograms will be performed at Screening, pre-dose on Day 1, and at 0.5 and 2 hours post-dose; ECGs will be performed at Follow-up only if necessary.
- Physical examination will be performed at Screening, Day -1 and at 24 hours post-dose; physical examinations will be performed at Follow-up only if necessary.
- Drugs of abuse and alcohol (breath test) Screening will be performed at Screening and Day -1.
- After the first dosing period of the study, a Follow-up Visit will take place 4 to 7 days after the final dose of lefamulin. This visit will also serve as the Screening Visit for the second dosing period. After the second dosing period, a Follow-up phone call will take place 4 to 7 days after the final dose of lefamulin to ensure the ongoing wellbeing of the patients. If a patient reports any TEAEs which represent a cause for concern (as determined by the Investigator) he/she will be required to attend the clinic for a Follow-up assessment. This will be considered an unscheduled visit.

Tolerability will be assessed by evaluation of the safety parameters and recorded adverse events.

Statistical methods:

Pharmacokinetics:

Presentation of PK data will be descriptive in nature and will be presented by treatment.

Appropriate non-compartmental techniques will be used to obtain estimates, including but not limited to, the following PK parameters (defined in the protocol) in plasma for lefamulin and the metabolite BC-8041 in plasma when possible and appropriate:

T_{lag} (oral dose only), T_{max}, C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24h)}$, $AUC_{(0\text{-}inf)}$, $AUC\%_{extrap}$, lambda-z, $t_{1/2}$, CL (IV dose only), CL/F (oral dose only), Vd (IV dose only), Vd/F (oral dose only), Vss (IV dose only), MRT, and (F).

Safety:

Safety and tolerability will be assessed by monitoring adverse events (AEs) and concomitant medications, clinical chemistry and hematology laboratory assessments, vital signs, ECG results, and physical examination findings. A complete description of the safety analysis variables will be presented in the Statistical Analysis Plan.

Table 1: Schedule of Assessments

Study Procedure	Screening[a]	IV Treatment Period and Oral Treatment Period											
		Day -1[b]	Day 1 pre-dose[c]	Day 1	Day 1 Post-dose								Follow-up[d]
					0.5 h	1 h	1.5 h	2 h	4 h	8 h	12 h	24 h	
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	

Table 1: Footnotes for Schedule of Assessments (Continued)

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 $\geq$ 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 ($\pm$ 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.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{\%extrap}$	Percentage of the area under the drug concentration curve due to extrapolation for infinity
$AUC_{0\text{-}12h}$	Area under the drug concentration curve from time zero (0 h) to 12 h
$AUC_{0\text{-}24h}$	Area under the drug concentration curve from time zero (0 h) to 24 h
$AUC_{0\text{-}inf}$	Area under the drug concentration curve from time zero (0 h) to infinity
$AUC_{0\text{-}last}$	Area under the drug concentration curve from time zero (0 h) to 24 h
β-hCG	beta-human chorionic gonadotropin
CABP	Community-acquired bacterial pneumonia
CF	Cystic fibrosis
CFR	Code of Federal Regulation
CFTR	Cystic fibrosis transmembrane conductance regulator (protein)
CL	Clearance, the apparent volume cleared for drug
CL/F	Total body clearance for extravascular administration
C_{max}	Maximum observed plasma concentration
CRF	Case report form
CRU	Clinical research unit
CV	Coefficient of variation
CYP3A	Cytochrome P450
DAC	Designated Activity Company
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
F	Oral bioavailability
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
h	Hour; hours
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International Council for Harmonisation
IR	Immediate-release
IRB	Institutional Review Board
IV	Intravenous
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
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
MedDRA	Medical Dictionary for Regulatory Activities
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRT	Mean residence time
N	Number
P-gp	P-glycoprotein
PK	Pharmacokinetic
PTC	Peptidyl transferase center
q12h	Every 12 hours
QA	Quality Assurance
QTcF	QT interval corrected according to Fridericia
rRNA	Ribosomal ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SUSAR	Suspected unexpected serious adverse event
$t_{½}$	Apparent elimination half-life calculated as $\ln(2)/k_e$
TEAE	Treatment-emergent adverse event
T_{lag}	The finite time taken for a drug to appear in systemic circulation following extravascular administration
t_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
Vd	Volume of distribution
Vd/F	Volume of distribution corrected for bioavailability
Vss	Volume of distribution at steady state
WHO	World Health Organization

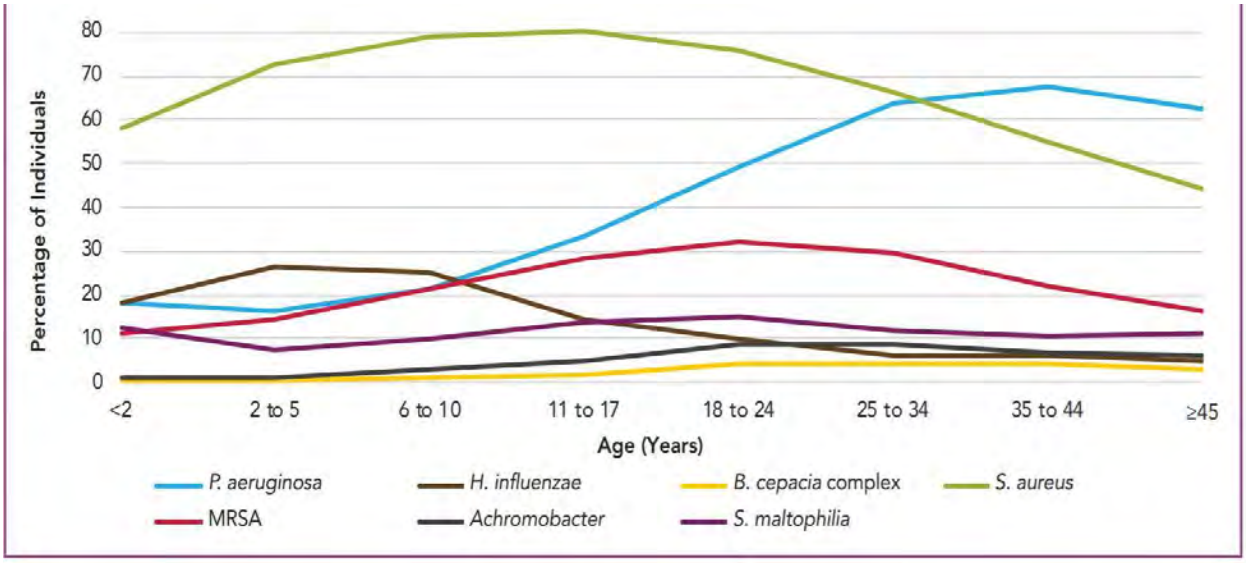
3. INTRODUCTION

3.1. Cystic Fibrosis

Cystic fibrosis (CF) is a genetic, autosomal recessive disease resulting from a mutation in a single gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein (Katkin, 2020). The CFTR gene encodes for the CFTR protein, which is located in every mucus-producing organ of the body, including the lungs, liver, pancreas, and intestines, as well as sweat glands. Normally, the CFTR protein controls the movement of ions from inside the cell to outside the cell. In people with CF, the mutated gene causes the protein to not work properly, which, in turn, affects the movement of sodium and water. This causes thick, sticky mucus and blockages in the lungs and digestive system.

Staphylococcus aureus is one of the most common airway pathogen in patients with CF (Figure 1). Airway infections are associated with progressive lung function decline and respiratory failure, which is the leading cause of mortality. Pulmonary exacerbations are aggressively managed with high health care utilization, requiring chronic treatment. Methicillin-resistant *S. aureus* (MRSA) is also associated with poor survival in CF patients. In patients with respiratory tract cultures positive for MRSA, median survival time is 6.2 years less than for patients with negative MRSA cultures. Therefore, MRSA infection may be a modifiable risk factor for death in patients with CF (Figure 2).

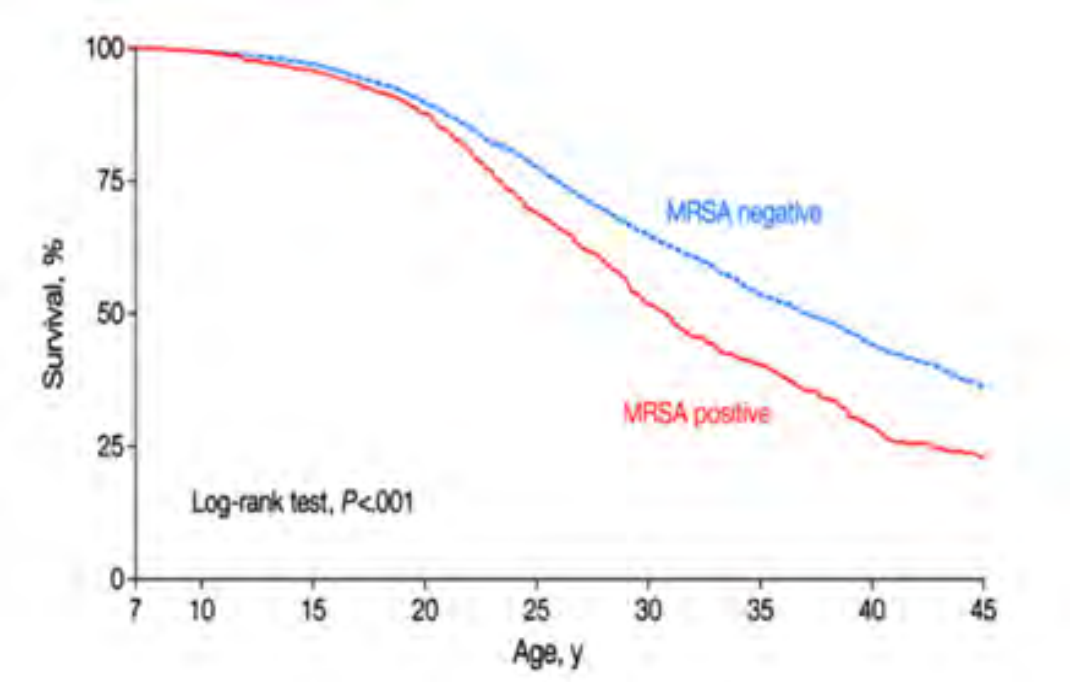
Figure 1: Prevalence of Respiratory Microorganisms by Age Cohort (2019)



MRSA = methicillin-resistant *Staphylococcus aureus*

Source: Cystic Fibrosis Foundation Patient Registry. Annual Data Report 2019.

Figure 2: Kaplan-Meier Estimates of Survival According to MRSA Status (N = 19,833 patients)



MRSA = methicillin-resistant Staphylococcus aureus; y = year
Source: Dasenbrook et al, 2010

While a number of anti-staphylococcal antibiotics are marketed, several major limitations exist regarding their utility in the management of bacterial exacerbations in patients with CF: 1) no agent has been demonstrated to have an acceptable efficacy and safety profile to result in marketing authorization approval by the Food and Drug Administration (FDA), European Medicines Agency (EMA), or other health authority for the treatment of exacerbations of CF caused by *S. aureus*; 2) the agents possessing appreciable activity against MRSA require parenteral administration; 3) agents such as trimethoprim-sulfamethoxazole, clindamycin, doxy/minocycline, that can be administered orally do not possess consistent activity against MRSA and have significant safety and tolerability issues limiting their utility in CF patients.

3.2. Lefamulin

XENLETA® (lefamulin; BC-3781), is a novel, semi-synthetic, first-in-class pleuromutilin antibiotic for systemic use in humans. Pleuromutilin derivatives inhibit bacterial protein synthesis by a novel interaction with the peptidyl transferase center (PTC) in domain V of 23S ribosomal ribonucleic acid (rRNA) in the large ribosomal subunit. The unique binding site of the pleuromutilins in the highly conserved core of the ribosomal PTC confers a low propensity for the development of bacterial resistance, and a lack of cross-resistance with other antibiotic classes. A pleuromutilin has been approved for topical use in humans and oral pleuromutilins have been used in veterinary medicine for many years.

In August 2019, the United States (US) FDA approved lefamulin in the treatment of community-acquired bacterial pneumonia (CABP) in adults 18 years of age and older caused by the following susceptible microorganisms: *Streptococcus pneumoniae, Staphylococcus aureus* (methicillin-susceptible isolates), *Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* (Nabriva Therapeutics, Inc., 2021). While the number of patients in the CABP pivotal program with MRSA did not result in an indication statement that includes MRSA, lefamulin has been demonstrated to possess excellent activity against MRSA in *in vitro* and *in vivo* animal infection models. In addition, lefamulin was shown to have similar efficacy as compared with intravenous (IV) vancomycin in a Phase 2 clinical study of the treatment of acute bacterial skin and skin structure infections in which approximately 69% of subjects had MRSA as the causative organism identified (Prince, 2013).

For details on lefamulin nonclinical and clinical development programs, see the current version of the Investigator's Brochure.

3.3. Study and Dose Rationale

Study NAB-BC-3781-1014 (hereafter referred to as Study 1014) is designed to evaluate the pharmacokinetics (PK) of a 600-mg immediate-release (IR) tablet and 150-mg IV formulations of lefamulin in adult patients with CF.

3.3.1. Study Rationale

Staphylococcus aureus is one of the most common causative pathogens associated with exacerbations of CF (Cystic Fibrosis Foundation, 2019). Current treatment guidelines for the management of exaccerbations of CF caused by *S. aureus* recommend the use of unapproved antibactertial agents. Further, many of the recommended treatments can only be administered via the IV route and/or have limitations due to safety and tolerability. Lefamulin is a novel, first-in-class, IV and oral pleuromutilin antimicrobial agent that has been demonstrated to be highly potent against *S. aureus*, including MRSA and strains obtained from patients with CF (Nabriva Therapeutics, Inc., 2021; Sader, 2021). Cystic fibrosis patients have altered drug distribution and elimination kinetics for many antimicrobials relative to patients without CF. While the advent of CFTR modulaotrs has resulted in improved lung function and had a positive impact on the quality of life of CF patients, limited data have been published describing the impact of the conomittnat use of CFTR modulaotrs and commonly used antibacterial agents (Albright, 2020).

This study is intended to assess the PK and safety of a single dose of IV and oral formulations of lefamulin in adults with CF.

3.3.2. Dose Rationale

For treatment of adults with CABP, the recommended dosage regimen of lefamulin is as follows:

- 150 mg every 12 hours (q12h) by IV infusion over 60 minutes for 5 to 7 days, or
- 150 mg q12h by IV infusion over 60 minutes then switch to 600 mg orally q12h (at the discretion of the physician) for 5 to 7 days total, or
- 600 mg orally q12h for 5 days.

In this study, single doses of IV and oral lefamulin will be studied in CF patients; PK data from this study will be sufficient to compare exposure in these patients to the known exposure in non-CF patients. The single doses to be evaluated in adults will be those recommended for treatment of CABP, ie, 150 mg IV or 600 mg orally.

3.4. Risk Assessment

Patients participating in this crossover study will receive lefamulin as a single 600-mg IR tablet and a 150-mg IV infusion in a crossover fashion for the purposes of PK and safety assessment. Consequently, patients participating in the study will be unlikely to derive any clinical benefit from exposure to lefamulin.

In adult clinical studies conducted to date, lefamulin has been well tolerated when administered by the oral and IV routes (see Investigator's Brochure, Section 5.2.1). Following oral dosing, gastrointestinal adverse events were most frequent (typically mild nausea, diarrhoea, or abdominal pain), without a clear correlation with dose level. Following IV dosing, the most frequently reported adverse events were administration site reactions. Analysis by dose showed that these events generally were more frequent at IV doses ≥ 150 mg. Thus, this study is expected to pose low risk to patients.

To minimize potential risk to individuals in this study there are strict inclusion and exclusion criteria. Potential patients will be carefully screened by laboratory evaluations, medical history, physical examination, and by electrocardiogram (ECG) to exclude those patients who could be at increased risk. Participating patients will be monitored for safety and tolerability during each part of the study and through a Follow-up phone call which will take place 4 to 7 days after the last dose of lefamulin in the second dosing period of the study.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Objectives

4.1.1. Primary Objective

- To evaluate the PK of a 600-mg IR tablet and 150-mg IV formulations of lefamulin in adult patients with CF

4.1.2. Secondary Objectives

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

4.1.3. Exploratory Objective

- To approximate the penetration of lefamulin into sputum in CF patients

4.2. Endpoints

4.2.1. 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.

Appropriate non-compartmental techniques will be used to obtain estimates, including but not limited to, the following PK parameters in plasma for lefamulin and its metabolite BC-8041 when possible and appropriate:

- C_{max}: maximum observed plasma concentration
- t_{max}: time to reach maximum plasma concentration of lefamulin following drug administration
- $AUC_{0\text{-}12h}$: area under the drug concentration curve from time zero (0 hour [h]) to 12 h
- $AUC_{0\text{-}24h}$: area under the drug concentration curve from time zero (0 h) to 24 h
- $AUC_{0\text{-}last}$: area under the drug concentration curve from time zero (0 h) to 24 h
- AUC_{∞} area under the drug concentration curve from time zero (0 h) to infinity
- $t_{½}$: apparent elimination half-life calculated as $\ln(2)/ k_e$
- CL: clearance (IV dose only)
- CL/F: total body clearance (oral dose only)
- T_{lag} (oral dose only): the finite time taken for a drug to appear in systemic circulation following extravascular administration
- $AUC_{\%extrap}$: percentage of AUC due to extrapolation for infinity

- 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
- Vd (IV dose only): volume of distribution
- Vd/F (oral dose only): volume of distribution corrected for bioavailability
- Vss (IV dose only): volume of distribution at steady state
- MRT: mean residence time
- F: oral bioavailability

4.2.2. Secondary Endpoints

- Descriptive summaries of the following:
  - Treatment-emergent adverse events (TEAEs)
  - Laboratory assessments (chemistry and hematology)
  - Vital signs measurements
  - Electrocardiogram parameters

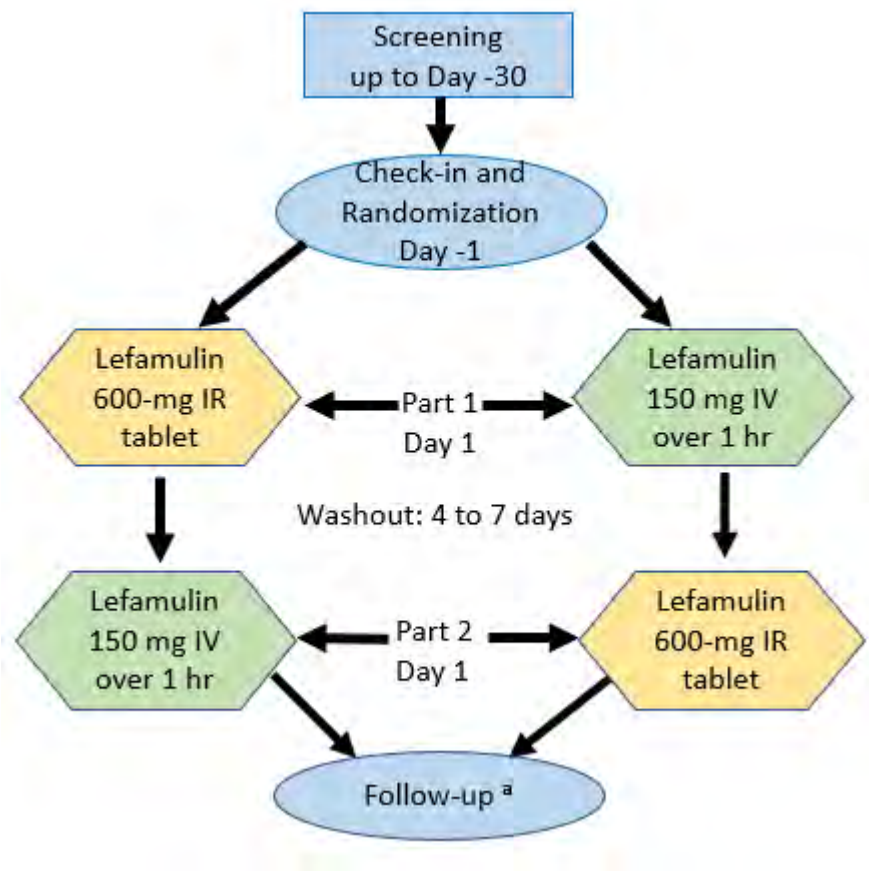
4.2.3. Exploratory Endpoint

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

5. INVESTIGATIONAL PLAN

This will be a single-cohort, open-label, randomized, 2-part, crossover study in patients with CF. In one dosing period, lefamulin will be administered as a 150 mg IV infusion in 250 mL citrate buffered saline over 1 hour. In the second dosing period, lefamulin will be administered as a 600-mg IR tablet orally in the fasted state. Study periods will be separated by 4 to 7 days. The overall study design is depicted in Figure 3.

Figure 3: Study Design



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.

Twelve adult patients with CF are planned to be enrolled. Patients will be screened for study eligibility up to 30 days before the first dose of study drug in the first dosing period (Day 1). For each period, eligible patients will remain at the clinical research unit (CRU) on Day -1 until collection of the 12-hour post-dose PK sample and safety assessments are completed. Patients will have the option to: 1) be discharged from the CRU after the 12-hour study procedures are completed; or 2) stay overnight in the CRU through the 24-hour study procedures. If a patient chooses to be discharged, he/she will be required to reurn to the CRU for the 24-hour study procedures to be completed.

After the first dosing period, a Follow-up Visit will be reassessed before each CRU admission. Patients will have a Follow-up phone call assessment take place 4 to 7 days after the final dose of lefamulin. This visit will also serve as the Screening Visit for the second dosing period. After the second dosing period, a Follow-up phone call will take place 4 to 7 days after the final dose of lefamulin to ensure the ongoing wellbeing of the patients.

Following Screening, total duration of study participation for each patient will be approximately 10 to 13 days (depending on the duration of the washout period).

6. 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.

6.1. Subject Inclusion Criteria

Potential patients must meet all of the following inclusion criteria to be eligible for participation in the study:

1. Signed informed consent.
2. Age ≥ 18 years of age.
3. Genetic confirmation of CF diagnosis will be by a report from a genetic test, such as "F508 deletion detected."
4. Weight > 40 kgs.
5. Forced expiration volume (FEV)1 > 40% predicted, as measured during the most recent evaluation.
6. Mentally and physically able to participate in the study as determined by the Investigator, ie, clinically stable with no significant changes in health status within 28 days prior to, and including, Day 1.
7. Vital signs within the following ranges:
    a. Tympanic temperature, < 38°C
    b. Systolic blood pressure, 90 to 160 mmHg
    c. Diastolic blood pressure, 50 to 90 mmHg
    d. Heart rate (HR) < 100 beats per minute at rest
    e. Respiration rate 12 to 20 breaths/min
    f. Oxygen saturation to be documented. No selection criteria; supplemental oxygen use is acceptable.
8. Negative beta-human chorionic gonadotropin (β-hCG) urine or serum pregnancy test for females of childbearing potential.
9. Willing to commit to acceptable methods of contraception as defined below.
    a. Female patients of childbearing potential must agree to use approved, highly effecive methods of contraception from the Screening Visit through the Follow-up Visit or phone call. These contraceptives include: true abstinence (when this is in line with the preferred and usual lifestyle of the patient), intrauterine devices with a failure rate of < 1%, or double barrier contraception (diaphragm with spermicide plus condom with spermicide).
    NOTE: A woman is assumed to be of childbearing potential unless one of the following criterion is met:
        – Underwent an acceptable method of surgical sterilization at least 6 months prior to the first dose.

- Has had amenorrhea for ≥ 12 months with follicle stimulating hormone (FSH) level > 40 mIU/mL.

b. Male patients must agree to use either true abstinence (when this is in line with the preferred and usual lifestyle of the patient) or double method of contraception (ie, condom with spermicide) from Screening through at least 90 days after the last dose of lefamulin.

6.2. Subject Exclusion Criteria

Potential patients meeting any of the following criteria will be excluded from the study:

1. Known history of chronic liver or biliary disease, Gilbert's syndrome, or or any of the following at Screening: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 x upper limit of normal (ULN), total bilirubin > 1.5 x ULN.
2. Prolonged baseline corrected QT interval corrected according to Fridericia (QTcF) defined as > 440 ms (females) and > 430 ms (males).
3. Family history or presence of prolonged QT syndrome, Torsades de Pointe, or known conduction defects (eg, bundle branch block, atrioventricular block).
4. Use of Orkambi® (lumacaftor/ivacaftor) within 28 days prior to Day 1.
5. Use of cytochrome P450 (CYP)3A substrates that prolong the QT interval within 24 hours prior to Day 1 (see Appendix 2).
6. Use of strong and moderate CYP3A inducers or P-glycoprotein (P-gp) inducers within 28 days prior to Day1 (see Appendix 2).
7. Use of strong inhibitors of CYP3A4 within 24 hours prior to Day 1 as described in Appendix 2.
8. Serum potassium levels below the normal reference range at Screening.
9. Known allergy to pleuromutilin class of antibiotic or any of the excipients of the lefamulin formulations.
10. Consumption of grapefruit, grapefruit juice, grapefruit products, pomelo, or Seville oranges within 24 hours before Day 1.
11. Use of vaporized nicotine or cannabidiol products, smoking (regularly or intermittently) more than 5 cigarettes (or equivalent) per day, or any use of tobacco other than in cigarettes or cigars within 28 days of Day 1.
12. Positive blood test for hepatitis C, human immunodeficiency virus (HIV), or hepatitis B antigen or core antibody (indicating active infection).
13. Positive test for drugs of abuse or alcohol at Screening or Day -1 that cannot be supported by medical history (eg, recent physician prescribed use of codeine).
14. Use of an investigational product within the 30 days prior to Day 1 (3 months prior to Day 1 if the study drug was a new chemical entity).
15. Difficulty swallowing tablets.

16. Females who are pregnant or breastfeeding.
17. Does not have suitable venous access for multiple venipuncture or cannulation.
18. Any medical, psychological, cognitive, social, or legal conditions that, in the opinion of the Investigator, would interfere with the patient's ability to give an informed consent and/or participate fully in the study.
19. Any other reason, in the opinion of the Investigator, the patient is unsuitable to participate.

7. STUDY DRUG ADMINISTRATION

7.1. Duration of Treatment

Each patient will receive a single dose of lefamulin at 2 study periods 4 to 7 days apart.

7.2. Timing of Dose and Dose Administration

Lefamulin 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.

7.3. Treatment Compliance

Study personnel will observe administration of each oral dose of lefamulin to each patient while at the investigative site. A mouth and hand check will be performed to ensure patients took the full dose provided. The study personnel will administer the IV infusion of lefamulin at the investigative site.

The dose and date/time of the administration of the study drug will be recorded in the site source documents and in the appropriate sections of the electronic case report form (eCRF).

7.4. Randomization

Randomization will be accomplished by using a pre-prepared randomization scheme at each site and assigning patients to treatment, sequentially at the site, according to the site's randomization table.

8. STUDY ASSESSMENTS AND PROCEDURES

A schedule of study assessments is provided in Table 1. Patients meeting all inclusion criteria and none of the exclusion criteria may be enrolled in the study after the nature and purpose of the protocol has been explained and written informed consent/assent has been voluntarily given by the patient or his/her legal representative, when appropriate.

Consent must be obtained before any screening procedures are performed and before study drug administration. All study assessments and procedures as specified in this protocol will be performed by the Investigator or a qualified designee.

Patients will be screened within 30 days before check-in to the CRU on Day -1. For patients who are screened (ie, those with signed written informed consent) but not enrolled, the reason for screening failure will be documented. If a patient is determined to be a screen failure, he/she can be rescreened once if the Investigator believes the patient will be eligible upon rescreening.

8.1. Medical/Surgical History

A medical and surgical history will be taken at Screening and on Day -1 of each Period. All medical history findings that have been present/active within 1 year before enrollment will be entered into the eCRF regardless of clinical relevance or presence at study start. Medical history findings that have been present within the 5 years before enrollment will be recorded if deemed clinically relevant by the Investigator to the conduct of the study. The medical history should include drug allergy history.

8.2. Physical Examinations

A complete physical examination (except for rectal and vaginal examinations) will be performed by the Investigator at Screening and upon check-in to the CRU on Day -1. At the other time points specified in Table 1, focused physical examinations will be performed according to standard institutional practices and must be documented in source documents. Clinically significant findings, as determined by the Investigator, will be documented in the eCRF as either medical history or adverse events.

Body weight and height will be measured at Screening only.

8.3. Vital Signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature, HR, respiratory rate, and oxygen saturation measurements will be recorded at the time points specified in Table 1.

Vital signs will be measured after patients have rested for at least 5 minutes in a sitting position. The position adopted by an individual patient should be consistent throughout the study. On Day 1 of each dosing period, pre-dose vital signs will be measured within 2 hours before each dose. If a patient has an abnormal value for SBP, DBP, or HR, the measurement may be repeated twice. If the second repeat measurement value does not qualify the patient, he or she is not eligible for that part of the study but may be reevaluated at a later time.

Vital signs measurements should be repeated if clinically significant changes or machine errors occur during the course of the study.

Sitting BP and/or HR (as applicable) will be measured more frequently if warranted by the clinical condition of the patient.

Vital signs will be measured using the same type of device throughout the study. Vital sign measurements will be recorded in the eCRF. Clinically relevant vital signs abnormalities meeting the definition of an adverse event (AE) must be recorded by the Investigator on the AE page of the eCRF.

8.4. Clinical Laboratory Tests (Safety)

Clinical chemistry and hematology assessments will be performed at the time points specified in Table 1. All safety laboratory tests performed during the study (Screening through Follow-up) will be analyzed at a local laboratory. Additional tests may be performed at the discretion of the Investigator if deemed clinically appropriate. A full list of the clinical laboratory tests that will be performed and analyzed can be found in Appendix 1.

A serum or urine pregnancy test will be performed on all females of childbearing potential at the Screening and Day -1 Visits for each dosing period. A confirmatory FSH level will be determined at Screening for females who are ≥ 1 year post-menopausal. A FSH level > 40 mIU/mL indicates non-child bearing potential.

Safety laboratory results outside the normal range will be evaluated by the Investigator as "clinically significant" or "not clinically significant." Any clinically significant value that is not expected for this population should be repeated as necessary.

If a patient has an abnormal laboratory value at check-in for either study period, the laboratory test may be repeated. If after the repeat measurement the value does not qualify the patient , the patient is not eligible for that part of the study. If the Investigator determines that the laboratory abnormality is likely to be transient and easily explained, the explanation will be documented and the patient may return once for re-evaluation after an appropriate time interval determined by the Principal Investigator at the time of the disqualifying laboratory result availability. Only a single re-evaluation will be accepted.

8.5. Electrocardiograms

A 12-lead ECG will be performed at the time points specified in Table 1 after the patient has been resting in a supine position for 10 minutes. The Day 1 pre-dose ECG must be reviewed by the Investigator or their designee before dosing to ensure that there are no clinically significant findings that would prevent dosing. Additional ECGs may be performed at the discretion of the Investigator or when clinically indicated.

If a patient has an abnormal value ECG at Screening for either of the parts of the study, the ECG may be repeated twice. If after the second repeat measurement the value does not qualify the patient, he or she is not eligible for dosing. If the patient has prolongation of the QTc interval or any arrhythmia during the post-dose ECGs, no further lefamulin should be administered.

8.6. Pharmacokinetics

8.6.1. Plasma Sample Collection

Blood samples will be taken for the measurement of PK parameters at the following time points in each part of the study (Table 1):

- Pre-dose; 30 min, and 1, 1.5, 2, 4, 8, 12, and 24 hours post-dose.

For details on sample collection, preparation, and shipment, refer to the study-specific Laboratory Manual supplied by the Sponsor. It is recommended that the blood samples are taken by a venipuncture or from a separate catheter, other than the catheter used for the infusion, to prevent any contamination of the PK blood samples with lefamulin from the infusion line and catheter.

Plasma samples will be analyzed for concentrations of lefamulin and its metabolite BC-8041 using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method at the bioanalytical laboratory.

The maximum total blood volume collected in the study for safety and PK evaluations is 36 mL per patient.

8.6.2. Sputum Sample Collection

Spontaneous sputum samples will be collected first thing in the morning on Day 1 (pre-dose), and as many times as possible that the patient can provide a sample until 24 hours after dosing for PK analysis of lefamulin. The exact time of sputum production will be recorded so the post-dose time can be determined precisely.

Any spontaneous production of sputum during inpatient observation will also be collected and the time of collection documented.

For details on sample collection, preparation, and shipment, refer to the study specific Laboratory Manual supplied by the Sponsor.

Sputum samples will be analyzed for concentrations of lefamulin using a validated LC-MS/MS method at the bioanalytical laboratory.

8.7. Prior and Concomitant Medications

Prior and concomitant medications, including prescription medications, dietary supplements/ vitamins, and over-the-counter medications will be recorded in the eCRF throughout the study. Topical medications will be recorded only if used as treatment for an adverse event. At a minimum, the drug name (preferably generic), dose, frequency, indication, and the start and stop dates of administration should be recorded.

Medications will be coded using the current version of the World Health Organization (WHO) Drug Dictionary.

8.7.1. Prior Medications

All medications taken within 14 days before Day -1 of the first treatment administration will be recorded in the eCRF.

8.7.2. Concomitant Medications

All medications (other than study drug) taken from Day 1 through the Follow-up Visit after the second dosing period will be recorded in the eCRF, including any medications used to treat an adverse event.

8.8. Restrictions During the Study

The following restrictions apply to all patients.

- No grapefruit, grapefruit juice, grapefruit products, pomelo, or Seville oranges from 24 hours before Day 1 until discharge from CRU in each part of the study.
- No excessive alcohol consumption (> 21 g alcohol per day for men and > 14 g alcohol per day for women) or use of alcohol from 48 hours before Day 1 until discharge from CRU in each part of the the study.
- No use of vaporized nicotine or cannabidiol products, smoking (regularly or intermittently) more than 5 cigarettes (or equivalent) per day, or any use of tobacco other than in cigarettes or cigars within 28 days of Day 1 through discharge from the CRU.

8.9. Discontinuation from Study Medication

Patients are free to withdraw from study medication at any time for any reason. Patients may be withdrawn from study medication at the discretion of the Investigator at any time. If a patient is discontinued from study medication, the reason for discontinuation will be collected in the eCRF.

A patient will be discontinued prematurely from the study medication for any of the following reasons:

- Patient request
- Lost to follow-up
- Death
- Physician decision (ie, assessment that it is not in the patient's best interest to continue, or other reason)
- Sponsor decision
- Positive drug/alcohol test
- Failure to meet eligibility criteria either part of the study

If a patient is prematurely discontinued from study medication, the Investigator should obtain a PK sample if possible and perform all procedures scheduled for discharge from the unit. The patient will be contacted for a Follow-up phone call 4 to 7 days from the time he/she is discharged from the unit to ensure the ongoing wellbeing of the patient. If a patient reports any AEs which represent a cause for concern, he/she will be required to attend the clinic for a Follow-up assessment. This will be considered an unscheduled visit. Any patient withdrawn from study medication due to an adverse event or clinically significant abnormal laboratory test

result will be evaluated by the Investigator, or a monitoring physician, and will be treated and/or followed until the symptoms or values have either resolved or are assessed as stable by the Investigator.

8.10. Discontinuation from Study

Patients are free to withdraw from the study at any time for any reason. Patients may be withdrawn from the study at the discretion of the Investigator at any time. If a patient is discontinued from the study, the reason for discontinuation will be collected in the eCRF.

A patient may be discontinued prematurely from the study for the following reasons:

- Withdrawal of consent by patient
- Adverse event
- Pregnancy
- Lost to follow-up
- Death
- Other (to be specified by the Investigator)

If a patient is prematurely discontinued from the study, the Investigator should obtain a PK sample if possible and perform all procedures scheduled for discharge from the unit. The patient will be contacted for a Follow-up phone call 4 to 7 days from the time he/she is discharged from the unit to ensure the ongoing wellbeing of the patient. If a patient reports any AEs which represent a cause for concern, he/she will be required to attend the clinic for a Follow-up assessment. This will be considered an unscheduled visit. Any patient withdrawn from study medication due to an adverse event or clinically significant abnormal laboratory test result will be evaluated by the Investigator, or a monitoring physician, and will be treated and/or followed until the symptoms or values have either resolved or are assessed as stable by the Investigator.

Every reasonable attempt should be made to retain patients in the study. If a patient does not report to the study site for a scheduled visit, study personnel will make 3 contact attempts: 2 telephone contact attempts and, if these are unsuccessful, a certified letter will be sent to the patient. The patient will be considered lost to follow-up if: (1) upon receipt of delivery confirmation of the certified letter the patient does not contact the site; or (2) the certified letter is returned as undeliverable.

9. ADVERSE EVENTS

9.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the investigational medicinal product.

Any pre-existing conditions or signs and/or symptoms present in a patient before the start of the study (ie, before informed consent) should be recorded as medical/surgical history. Any medical occurrences that are new or worsened from the time of informed consent and up to and including the final visit must be reported as AEs. All AEs must be recorded regardless of causality.

Patients will be monitored throughout the study for adverse reactions to the study medications and/or procedures at each study visit. Questions will be posed in a non-leading manner so as not to bias the response. In addition to questioning at specific time points, patients will be encouraged to spontaneously report any AEs. Any patient with an AE or clinically significant abnormal laboratory test result will be evaluated by the Investigator, or a monitoring physician, and will be treated and/or followed until the symptoms or values have resolved or are assessed as stable by the Investigator. A physician, either at the investigative site or at a nearby hospital emergency room, will administer treatment for any serious adverse events (SAEs). When appropriate, medical tests and examinations may be performed to ensure an AE has fully resolved.

Adverse events will be collected throughout the study from the time a patient signs the informed consent through the Follow-up assessment after the second dosing period. Whenever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF.

The Investigator will evaluate and report the onset date/time, outcome and end date/time, severity (intensity), relationship to study drug, actions taken with study drug, whether event caused study discontinuation, whether concomitant or additional treatment was given, and determination of seriousness for each AE.

Laboratory abnormalities will not be considered AEs unless they are associated with clinical signs and symptoms or require medical intervention. Clinically significant abnormal clinical laboratory findings, unless judged by the Investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs.

The Investigator will exercise medical and scientific judgment in deciding whether an abnormal clinical laboratory finding or other abnormal assessment is clinically significant.

9.2. Assessment of Severity (Intensity)

The following definitions for rating severity (intensity) will be used:

- **Mild**: An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: An AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but the patient is still able to function.
- **Severe**: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.3. Assessment of Relationship to Study Drug

The Investigator will use his/her clinical judgment to explain each AE and determine its relationship, if any, to study drug treatment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will also consult the Investigator's Brochure in the determination of his/her assessment. Causality should be assessed using the following categories:

- **Not related:** The event could readily be explained by factors not involving the study drug and a temporal relationship with the study drug did not exist.
- **Possibly Related:** There was some temporal relationship between the event and the administration of the study drug and the event was unlikely to be explained by the patient's medical condition or other therapies.
- **Probably Related:** The temporal relationship between the event and the administration of the study drug was suggestive, and the event was less likely to be explained by the patient's medical condition or other therapies.
- **Definitely Related:** The event followed a reasonable temporal sequence from administration of the study drug, followed a known or suspected response pattern to the study drug, was confirmed by improvement upon stopping the study drug (dechallenge) and reappeared upon repeated exposure (rechallenge). (NOTE: this is not to be construed as requiring re-exposure of the patient, however, a category of definitely related could only be used when recurrence was observed.).

9.4. Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening. NOTE: The term 'life-threatening' in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Results in persistent or significant disability/incapacity.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

NOTE: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after entry into the study, should not be classified as SAEs. For example, admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).

- Is a congenital anomaly/birth defect.
- Is an important medical event.

NOTE: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

All SAEs occurring from the time of informed consent through completion of the Follow-up assessment after the second dosing period must be reported to Nabriva Therapeutics DAC or their representative within 24 hours of the knowledge of the occurrence (this refers to any AE that meets 1 or more of the aforementioned serious criteria). Reporting is done by completing the SAE form electronically in the Electronic Data Capture (EDC) system or paper SAE report form, whichever is applicable. The EDC system and/or paper report forms should be completed in as much detail as possible but lack of complete information should not delay the reporting of the SAE.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Nabriva Therapeutics DAC, or their representative. However, it is very important that the Investigator always makes an assessment of causality for every event prior to transmission of the SAE report form to Nabriva Therapeutics DAC, or their representative. The Investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report form accordingly. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The Investigator will provide the assessment of causality per instructions on the SAE form in the eCRF. Serious AEs determined by the Investigator to be related to the study drug must be reported even if more than 30 days after the last administration of study drug have elapsed. In addition, the Sponsor will also assess causality of SAEs based on the information provided by the Investigator.

All SAEs and suspected unexpected serious adverse events (SUSARs) will be reported by the Sponsor to the relevant competent authorities in accordance with the European Directive 2001/20/EC, as applicable.

Sponsor Safety Contact Information:

PI
PI , Drug Safety and Pharmacovigilance
PI

9.5. Other Reportable Events

Certain events should be reported to the Sponsor as Other Reportable Events. These include the following:

- Pregnancy exposure (a patient becomes pregnant while taking study drug)

  Patients who are pregnant at Screening and/or Day -1 are not permitted to participate in this study. Nabriva Therapeutics DAC or their representative must be notified of any female patient (or the partner of a male patient) who becomes pregnant during the study. Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator or designee to report any pregnancy that occurs during this study to Nabriva Therapeutics DAC or their representative.

- Lactation exposure (ie, the patient was taking study drug while nursing an infant)
- Accidental exposure (someone other than the study patient was exposed to study drug)
- Overdose (the patient received more than the prescribed dose of study drug within a given timeframe)
- Other medication errors that potentially place patients at a greater risk of harm than was previously known or recognized (eg, study drug was administered by an incorrect route)

10. DRUG SUPPLIES

10.1. Description of Drug Products

The active substance being investigated in this study is lefamulin (BC-3781), present in the drug product as the acetate salt (BC-3781.Ac). Physicochemical properties can be found in the Lefamulin Investigator's Brochure.

The IV drug product is supplied by the Sponsor in clear glass vials containing a sterile concentrate of the acetate salt of lefamulin (BC 3781.Ac) in normal saline. The content of one vial equals to 150 mg lefamulin free base. Lefamulin for IV use is constituted from one lefamulin 15 mL sterile concentrate vial into a sterile custom-manufactured 250 mL citrate buffered normal saline bag pH 5 for IV administration.

Oral lefamulin is supplied by the Sponsor as 600 mg blue, oval, film-coated, immediate-release tablets printed with "LEF 600" on one side.

Details of the qualitative and quantitative composition of lefamulin IV drug product and lefamulin 600-mg IR tablets are provided in the Lefamulin Investigator's Brochure.

10.2. Packaging and Labeling

Lefamulin will be packaged and labeled in accordance with the applicable regulatory authority requirements.

10.3. Storage of Study Drugs

Access to all study drugs must be restricted to designated study personnel throughout the study.

The lefamulin IV drug product is supplied in clear glass vials. The shelf life of the lefamulin concentrate vials is 48 months at 2 to 8°C. Commercial supplies of citrate buffered normal saline will be used.

The lefamulin 600-mg IR tablets will be supplied in a high-density polyethylene bottle with 30 tablets per bottle. The shelf life of the IR tablets is at least 48 months at controlled room temperature (15°C to 25°C).

Temperature excursions must be reported to the Sponsor.

10.4. Product Accountability

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study site personnel must maintain study drug accountability records throughout the course of the study. This person(s) will document the amount of study drug received from the supplier, the amounts dispensed to patients as well as lot numbers and expiration / retest date of study medications. At conclusion of the study, any unused study drug will be destroyed at the site after approval from the Sponsor. If no supplies remain, this will be recorded in the drug accountability section of the final monitoring report.

10.5. Compliance

Study personnel will supervise, observe, and record all study drug dosing of each patient while he/she is an inpatient at the CRU.

10.6. Treatment of Overdose

As study personnel are administering and documenting all doses in the study, the risk of overdose is considered to be low.

No specific antidote to lefamulin is known. Any signs or symptoms of a possible overdose will be treated supportively. In the case of an emergency, standard emergency procedures will be employed.

10.7. Occupational Safety

Lefamulin is not expected to pose a significant occupational safety risk to site staff under normal conditions of use and administration. Material Safety Data Sheets describing occupational hazards and recommended handling precautions will be either provided to the Investigator, where this is required by local laws, or are available upon request from Nabriva Therapeutics.

In line with good handling of chemical products, precautions are to be taken to avoid eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure, any signs or symptoms should be treated appropriately, and the Sponsor notified.

11. STATISTICAL ANALYSIS

11.1. Sample Size Determination

Target enrollment for this study will be 12 patients.

11.2. Analysis Sets

- Safety analysis set: All patients who received any dose of lefamulin.
- Pharmacokinetic analysis set: All patients who receive any dose of lefamulin and have an evaluable PK profile.

11.3. Variables for Analysis

11.3.1. Pharmacokinetic Analysis Variables

Appropriate non-compartmental techniques will be used to obtain estimates, including but not limited to, the following PK parameters in plasma for lefamulin and its metabolite BC-8041 when possible and appropriate: T_{lag} (oral dose only), T_{max}, C_{max}, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24h)}$, $AUC_{(0\text{-}inf)}$, $AUC_{\%extrap}$, lambda-z, $t_{1/2}$, CL (IV dose only), CL/F (oral dose only), Vd (IV dose only), Vd/F (oral dose only), Vss (IV dose only), MRT, and (F).

A complete description of the PK analysis variables will be presented in the Statistical Analysis Plan (SAP).

11.3.2. Safety Analysis Variables

Safety and tolerability will be assessed by monitoring AEs and concomitant medications, clinical chemistry and hematology laboratory assessments, vital signs, ECG results, and physical examination findings. A complete description of the safety analysis variables will be presented in the SAP.

11.4. Pharmacokinetic Analysis

Presentation of PK data will be descriptive in nature and will be presented by treatment.

11.5. Statistical Analysis

A separate SAP will be developed and approved before the final analyses. A complete description of the analyses will be provided in the SAP.

Categorical data will be summarized with counts and percentages and continuous variables with N, mean, coefficient of variation (CV), median, standard deviation, and range. In addition, PK parameters will be summarized with the geometric mean and geometric CV.

Further details of the statistical analysis will be provided in a study-specific SAP, which will include, but are not limited to:

- Definition of analysis populations
- Details of planned analysis of primary and secondary variables as well as safety

- Data handling conventions

11.6. Safety Analysis

Descriptive summaries and listings of individual patient safety data will be presented by treatment.

Safety will be evaluated in the Safety Analysis Set by presenting summaries of AEs, routine clinical laboratory parameters, ECG results, and vital sign parameters by treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables will be provided for all TEAEs. A TEAE is defined as an AE with a start date and time on or after study drug administration. The number and percentage of patients with TEAEs will be tabulated by system organ class and MedDRA preferred term for each treatment and dose, and by severity and relationship to treatment.

Treatment-emergent AEs leading to premature discontinuation from study and serious TEAEs will be presented in a table and/or a listing.

Safety data including clinical laboratory parameters, ECG results and vital signs will be summarized by treatment and scheduled assessment. These summaries will also include change from baseline for each scheduled assessment by treatment.

12. STUDY MONITORING

All aspects of the study will be carefully monitored by the Sponsor's authorized individuals, acting as agents of the Sponsor with respect to current Good Clinical Practice (GCP) and Standard Operating Procedures for compliance with applicable government regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

Frequent communication between the study site and the Sponsor is essential to ensure that the patient safety is monitored adequately. The Investigator will make safety assessments on an ongoing basis. The Sponsor's medical monitor will review safety information from all study sites as it becomes available throughout the study.

13. INSTITUTIONAL REVIEW BOARD APPROVAL

The Principal Investigator agrees to provide the Institutional Review Board (IRB) with all appropriate material, including a copy of the informed consent. The study will not be initiated until the Investigator obtains written approval of the research plan (protocol) and the informed consent document from the appropriate IRB and copies of these documents are received by Nabriva Therapeutics.

It is the Investigator's responsibility to obtain IRB approval for all subsequent major changes to the protocol, in compliance with local law. Appropriate reports on the progress of this study will be made by the Investigator to the IRB and Sponsor in accordance with applicable government regulations and in agreement with policy established by the Sponsor.

14. ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in compliance with this protocol, the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, October 2013), the guidelines of International Council on Harmonisation (ICH) GCP (CPMP/ICH/135/95), European Union (EU) Clinical Trials Directive 2001/20/EC, EU Commission Directive 2005/28/EC, and Code of Federal Regulation (CFR) Title 21, CFR Part 50, 56 and 312, designated Standard Operating Procedures, and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

15. INFORMED CONSENT

The ICH has issued guidelines to provide protection for human patients in clinical investigations. The ICH Tripartite Guideline for Good Clinical Practice establishes the general requirements for informed consent.

A properly executed, written informed consent in compliance with the terms of these guidelines shall be obtained from each patient before entering the study, or before performing any unusual or non-routine procedure in relation to the study. The purpose of the study, procedures to be carried out, and potential hazards will be described to each potential patient in non-technical terms. Patients will be required to read, voluntarily sign, and date an informed consent form summarizing the discussion at Screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will sign and date one copy of the informed consent form which will be photocopied. The copy will be retained by the patient and the original will be retained on file by the Investigator. The consent form must be approved by the appropriate IRB and Sponsor before study initiation at a study site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB and Sponsor before implementation.

16. QUALITY ASSURANCE/QUALITY CONTROL

Standard Operating Procedures belonging to Nabriva Therapeutic or designee(s) will be adhered to for all activities relevant to the quality of the study and are routinely monitored by the Quality Assurance (QA) Division.

Data will undergo quality control checks before clinical database lock. Sponsor-designated, independent monitors will be responsible for the monitoring of the study and its data within the eCRFs.

A QA audit of this study may be conducted by the Sponsor or Sponsor's designee. The QA auditor will have access to all medical records, the Investigator's study-related files and correspondence, and information in the informed consent documentation of this study.

An inspection of this study may be conducted by a regulatory agency. The Investigator agrees to contact the Sponsor as soon as possible, but not later than within 1 week, upon notification of an inspection by a regulatory agency. The Investigator agrees to allow the Inspector direct access to all relevant documents and to allocate his/her time and that of study site personnel to the

Inspector to discuss findings in any relevant issues. The Investigator will allow Sponsor personnel to be present as an observer during a regulatory inspection, if requested.

17. DATA HANDLING AND RECORD KEEPING

17.1. Data Handling

Electronic case report forms are produced, stored electronically, and are available to the designated study team members. Each eCRF is reviewed and signed by the Investigator. The final signed case report forms (CRFs) are provided to the Sponsor in the format as decided upon by the Sponsor, as documented in the data management plan (if applicable).

17.2. Subject Confidentiality

Investigator and his/her staff will be required to manage patient data collected for the study in accordance with applicable laws and regulations on personal data protection.

All US-based investigational sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. An investigational site that is not a Covered Entity as defined by HIPAA must provide documentation of this fact to Nabriva Therapeutics.

After patients have consented to take part in the study their medical records and the data collected during the study will be reviewed by Nabriva Therapeutics or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of Nabriva Therapeutics; third parties with whom Nabriva Therapeutics may develop, register or market lefamulin; national or local regulatory authorities and the IRBs that gave approval for this study to proceed.

Patients will be known by a unique number; however, their date of birth can also be collected if not in contradiction with any requirements and used to assist Nabriva Therapeutics to verify the accuracy of the data, for example, that the laboratory results are assigned to the correct patient. The results of this study may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection that applies within the EU. The purpose of any such transfer would be to support regulatory submissions in other countries.

17.3. Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

17.4. Data Entry

Data must be recorded using the eCRF as the study is in progress. All study site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with the Title 21 CFR Part 11 for US sites and EU Directives 2001/20/EC and 2005/28/EC for EU sites. All passwords will be strictly confidential.

17.5. Data Validation

Validation checks will be performed as agreed to in the Data Validation Plan.

17.6. Record Keeping

Raw data generated in connection with this study as well as an original copy of the final clinical study report, will be retained in archive until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of lefamulin. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

As required under European Directive 2005/28/EC, Article 17, all 'essential documents' (as described in the ICH GCP Guidelines) must be retained by Nabriva Therapeutics and the Investigator for at least 5 years after the completion of the clinical study. Therefore, all studies, independent of where they were conducted in the world, must follow this requirement in the event a submission is ever made in the EU. These documents may be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Nabriva Therapeutics. It is the responsibility of Nabriva Therapeutics to inform the Investigator as to when these documents no longer need to be retained. The Investigator must obtain written permission from Nabriva Therapeutics before the destruction of any study document.

The retention of investigator study records is an Investigator responsibility and Nabriva Therapeutics will neither arrange nor pay for this activity. Any transfer of ownership of the content of the clinical trial master file is the responsibility of the Investigator or site representative, and shall be documented. The new owner shall assume the responsibilities set forth in the applicable regulations.

These records must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the US FDA in accordance with 21 CFR 312.68 or other national or foreign regulatory authorities in accordance with regulatory requirements.

18. TERMINATION OF STUDY

The Sponsor reserves the right to discontinue this study at any time.

19. FINANCING AND INSURANCE

The costs necessary to perform the study will be agreed upon with each Investigator and will be documented in a separate financial agreement that will be signed by the Investigator and Nabriva Therapeutics (or designee), before the start of the study.

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the results or outcome of the study. The following information will be collected: any significant payments of other sorts from Nabriva Therapeutics, (eg, money to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria); any proprietary interest in lefamulin; any significant equity interest in Nabriva Therapeutics as defined in 21 CFR 54 2(b). In

consideration of participation in the study, Nabriva Therapeutics will pay the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

20. PUBLICATION POLICY

It is intended that the results of the study may be published as scientific literature. Results may also be used in submissions to Regulatory Authorities. The following conditions are to protect commercial confidential materials (eg, patents, etc.), not to restrict publication.

All information concerning lefamulin (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by Nabriva Therapeutics and not previously published) is considered confidential by Nabriva Therapeutics and shall remain the sole property of Nabriva Therapeutics. The Investigator agrees not to use it for other purposes without Nabriva Therapeutics written consent.

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Nabriva Therapeutics in advance of submission. The review is aimed at protecting Nabriva Therapeutics proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data shall be set out in the agreement between each Investigator and Nabriva Therapeutics.

21. REFERENCES

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APPENDIX 1. CLINICAL LABORATORY TESTS (SAFETY)

Hematology
Red blood cell count White blood cell count Hematocrit Hemoglobin Platelet count Differential count
Chemistry
Blood urea nitrogen Creatinine Glucose Sodium Potassium Chloride Bicarbonate Calcium Phosphorus Magnesium Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Creatine phosphokinase Total bilirubin Albumin Total protein
Other tests
Pregnancy test (serum or urine) – women of childbearing potential Follicle stimulating hormone (at Screening) – women who are ≥ 1 year post-menopausal Viral serology (at Screening): • HCVAb Ab (if positive, qualitative HCV RNA to test for active infection) • Hepatitis B surface antigen (HBsAg) • HIV Ab/HIV p24 Ag Urine drug screen – including but not limited to amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methamphetamine, opioids, and phencyclidine (PCP) Alcohol urine/breath test

APPENDIX 2. INTERACTING MEDICATIONS

XENLETA is classified as a moderate CYP3A inhibitor with mild inhibition potential for CYP2C8, but no induction potential. When administered orally, XENLETA may increase the plasma concentrations of drugs that are primarily metabolized by CYP450 3A4. No interaction on P-gp or significant interactions with other drug transporters has been observed or predicted. XENLETA is a substrate to CYP3A. The table below provides examples of potential co- medications and is not intended to be an exhaustive list.

XENLETA Injection		
Strong or moderate CYP3A inducers or P-gp inducers	eg, lumacaftor, rifampicin, St. John´s wort (*Hypericum perforatum*), rifabutin, phenobarbital, carbamazepine, phenytoin, bosentan, efavirenz, primidone	Avoid XENLETA Co-medication could significantly decrease lefamulin plasma concentration.
Drugs associated with QT interval prolongation	eg, moxifloxacin, disopyramide, doxepin, erythromycin, droperidol, salmeterol	Avoid XENLETA Co-medication could cause QT-interval prolongation
XENLETA Tablets		
Strong or moderate CYP3A inducers or P-gp inducers	eg, lumacaftor, rifampicin, St. John´s wort (*Hypericum perforatum*), rifabutin, phenobarbital, carbamazepine, phenytoin, bosentan, efavirenz, primidone	Avoid XENLETA Co-medication could significantly decrease lefamulin plasma concentration.
Strong CYP3A inhibitors or P-gp inhibitors	eg, clarithromycin, diltiazem, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, ritonavir-containing regimens, voriconazole, telithromycin	Avoid XENLETA Co-medication could significantly decrease lefamulin plasma concentration. significantly increase lefamulin plasma concentration.
Moderate CYP3A inhibitors or P-gp inhibitors	eg, fluconazole, zolpidem, ciprofloxacin, erythromycin	Record time and dose of co-medication. Could slightly increase lefamulin plasma concentration.
Drugs associated with QT interval prolongation	eg, moxifloxacin, disopyramide, doxepin, erythromycin, droperidol, salmeterol	Avoid XENLETA Co-medication could cause QT-interval prolongation
CYP3A substrates that prolong the QT interval	eg, pimozide, quinidine	Avoid XENLETA Concomitant use is contraindicated.
Sensitive CYP3A substrates or those that demonstrate a narrow therapeutic index	eg, midazolam, tacrolimus, ergot alkaloids, colchicine, fentanyl, macrolide immunosuppressants	Monitor for adverse reactions. No impact on plasma concentration of lefamulin.