Official Title: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Treatment, Two-Period Crossover Efficacy and Safety Study in Idiopathic Pulmonary Fibrosis with Nalbuphine ER Tablets for the Treatment of Cough

NCT Number: NCT04030026

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Trevi Therapeutics, Inc.

A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Treatment, Two-Period Crossover Efficacy and Safety Study in Idiopathic Pulmonary Fibrosis with Nalbuphine ER Tablets for the Treatment of Cough

Protocol Number:	TR12
Investigational Product:	Nalbuphine Extended-Release Tablets (NAL ER)
EudraCT Number:	2018-004744-31
Development Phase:	2
Sponsor Name and Address:	Trevi Therapeutics, Inc. 195 Church Street, 14th Floor New Haven, CT 06510 USA
Responsible Medical Officer:	[redacted] MD
Sponsor Contact:	[redacted]
Version:	Version 7.0
Protocol Date:	14 December 2021

1 PROTOCOL SYNOPSIS

Name of Sponsor/Company: Trevi Therapeutics, Inc.	**Name of Product:** Nalbuphine Extended-Release Tablets	**Name of Active Ingredient:** Nalbuphine HCl
Title of Study: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Treatment, Two-Period Crossover Efficacy and Safety Study in Idiopathic Pulmonary Fibrosis with Nalbuphine ER Tablets for the Treatment of Cough		
Study Centers: Up to 15 centers		
Publication(s): None		
Planned Study Period: May 2019 to March 2022	**Development Phase:** Phase 2	

Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of nalbuphine extended-release (NAL ER) tablets in the study population.
- To evaluate the effect of NAL ER tablets on the mean daytime cough frequency (coughs per hour) at Day 22 (dose 162 mg twice daily [BID]) as compared to placebo. Assessment is done using objective digital cough monitoring. Daytime is defined as the time the subject is awake in the 24 hours after the digital cough monitor is applied for use.

Secondary Objectives:

- To evaluate the effect of NAL ER tablets on the mean relative change from baseline in 24-hour (combined daytime and nighttime) cough frequency (coughs per hour) at Day 22 (dose: 162 mg BID).
- To evaluate the effect of NAL ER tablets on the mean relative change from baseline in nighttime cough frequency (coughs per hour) at, and Day 22 (dose: 162 mg BID).
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline on the Evaluating Respiratory Symptoms (E-RS™) diary cough scale (E-RS diary question number 2) by treatment at Days 9, 16, and 22.
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline in the Cough Severity Numerical Rating Scale by treatment at Days 8, 15, and 21.
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline in the E-RS diary breathlessness scale (E-RS diary questions 7, 8, 9, 10, and 11) by treatment at Days 9, 16, and 22.
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline in the 14-item the EXAcerbation of Chronic pulmonary disease Tool (EXACT®) version 1.1 e-diary tool total score by treatment at Days 9, 16, and 22.
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline in the Patient Reported Outcomes Measurement Information System (PROMIS®) Item Bank v1.0 Fatigue Short Form 7a scale by treatment at Day 21.

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- To evaluate the change in the Clinical Global Impression of Change (CGI-C) over time by treatment measured at Day 21.

Methodology:

This is a double-blind, randomized, placebo-controlled, 2-treatment, 2-period crossover efficacy and safety study in IPF subjects with NAL ER tablets for the treatment of cough. The study consists of 2 treatment periods of 3 weeks, each followed by a washout period of 2 weeks.

During Treatment Period 1, eligible subjects will be randomized (1:1) to one of the following treatment arms:

- **Arm 1:** Active NAL ER tablets followed by crossover Placebo tablets in Treatment Period 2
- **Arm 2:** Placebo tablets followed by crossover NAL ER tablets in Treatment Period 2

Following 3 weeks of dosing in Treatment Period 1, subjects will complete a 2-week washout period before entering Treatment Period 2. Subjects assigned to Arm 1 will receive placebo tablets and subjects assigned to Arm 2 will receive NAL ER tablets during Treatment Period 2. A final 2-week washout period will occur at the completion of Treatment Period 2.

NAL ER Dosing

Subjects on NAL ER tablets will have the dose titrated from 27 mg once daily (QD) to 54 mg BID over a 5-day period and then maintained at 54 mg BID for approximately 4 days. Doses will be subsequently escalated and maintained at 108 mg BID over 1 week and then to 162 mg BID over 6 days.

Study Visits

Study visits will include screening to determine eligibility, and for each treatment period: visits at Day -1 for baseline assessments, at Days 8, 15, and 21 during treatment, and a follow-up at the end of the 2-week washout period. At study screening and the Day 21 visits, during each treatment period, subjects will have blood drawn for safety analysis. Pharmacokinetic (PK) analysis of nalbuphine plasma concentration will also be done at Day 21. Subjects will complete questionnaires for efficacy evaluations and undergo safety evaluations including an ECG. At the baseline and Day 21 visits, during each treatment period, site staff will place an electronic cough monitor on the subject, which will be worn until the evening of the following day in order to obtain at least a full 24-hour recording period of cough frequency. At the end of each recording session, the monitor will be removed at home by the subject prior to bedtime. Subjects will complete a daily e-diary twice per day.

Subjects who discontinue investigational product, for reasons other than withdrawal of consent, will be considered to have prematurely discontinued treatment and will be asked to complete the premature discontinuation and 2-week off-treatment safety follow-up evaluations.

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Figure: Study Schematic

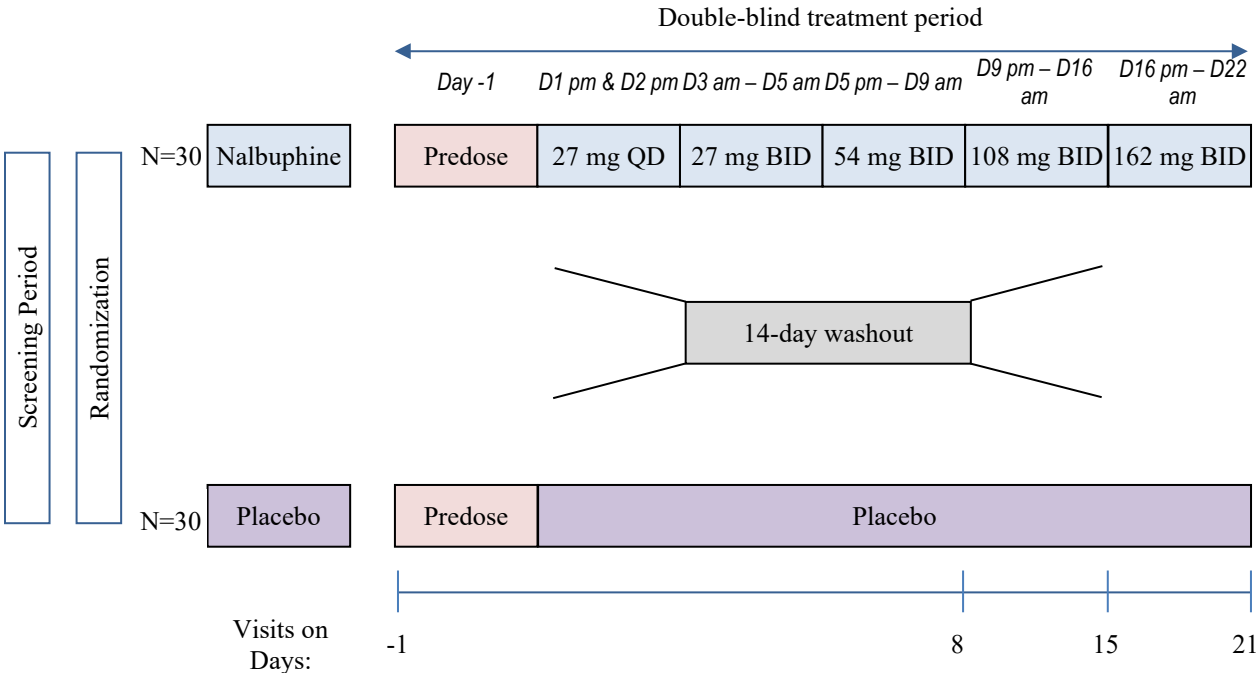

Table: Dosing Scheme

Treatment Period	Visit No.	Treatment Day	Dose (mg)			
			Arm 1		Arm 2	
			AM	PM	AM	PM
Treatment Period 1	2	-1	—	—	—	—
		1	—	27	—	Placebo
		2	—	27	—	Placebo
		3	27	27	Placebo	Placebo
		4	27	27	Placebo	Placebo
		5	27	54	Placebo	Placebo
		6	54	54	Placebo	Placebo
		7	54	54	Placebo	Placebo
	3	8	54	54	Placebo	Placebo
		9	54	108	Placebo	Placebo
		10	108	108	Placebo	Placebo
		11	108	108	Placebo	Placebo
		12	108	108	Placebo	Placebo
		13	108	108	Placebo	Placebo
		14	108	108	Placebo	Placebo
	4	15	108	108	Placebo	Placebo
		16	108	162	Placebo	Placebo
		17	162	162	Placebo	Placebo
		18	162	162	Placebo	Placebo
		19	162	162	Placebo	Placebo
		20	162	162	Placebo	Placebo
	5	21	162	162	Placebo	Placebo
		22	162	—	Placebo	—
2-Week Washout						
Treatment Period 2	6	-1	—	—	—	—
		1	—	Placebo	—	27
		2	—	Placebo	—	27
		3	Placebo	Placebo	27	27
		4	Placebo	Placebo	27	27
		5	Placebo	Placebo	27	54
		6	Placebo	Placebo	54	54
		7	Placebo	Placebo	54	54
	7	8	Placebo	Placebo	54	54
		9	Placebo	Placebo	54	108
		10	Placebo	Placebo	108	108
		11	Placebo	Placebo	108	108
		12	Placebo	Placebo	108	108
		13	Placebo	Placebo	108	108
		14	Placebo	Placebo	108	108
	8	15	Placebo	Placebo	108	108
		16	Placebo	Placebo	108	162
		17	Placebo	Placebo	162	162
		18	Placebo	Placebo	162	162
		19	Placebo	Placebo	162	162
		20	Placebo	Placebo	162	162
	9	21	Placebo	Placebo	162	162
		22	Placebo	—	162	—
2-Week Washout						

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Number of Subjects:
Approximately 60 subjects with diagnosed IPF will be randomized to ensure evaluable data from at least 44 subjects who complete both treatment periods.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Subjects eligible for randomization to receive investigational product must meet all the following criteria:

1. Diagnosis of "definite" or "probable" IPF based on ATS/ERS/JRS/ALAT criteria (see *Raghu et al 2018 in Appendix 6*).
2. Forced vital capacity (FVC) > 40% predicted of normal.
3. Diffusing capacity of the lung for carbon monoxide corrected for hemoglobin [DL_{CO}] > 25% predicted of normal within the past 6 months. Subjects who have not had DLco testing may be enrolled with medical monitor approval.
4. Chronic cough > 8 weeks.
5. Adequate swallow reflex as assessed by the ability to sip 3 fluid oz (or 89 ml) of water without coughing or choking.
6. Daytime cough severity score ≥ 4 on Cough Severity Numerical Rating Scale at screening.
7. Males or females age 18 years and older at the time of consent.
8. Females of childbearing potential must use an acceptable method of birth control (if sexually active). All females of childbearing potential must have a negative pregnancy test at the screening and baseline visits.

   For the purpose of this study, all females are considered to be of childbearing potential unless they are postmenopausal (i.e., at least 1 year since last menses and age > 50 years) or surgically sterile (i.e., tubal ligation, hysterectomy, and/or bilateral oophorectomy).

   Sexually active female subjects of childbearing potential are required to use 1 barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to 1 other method (e.g., intrauterine device in place for at least 1-month, stable hormonal contraception for at least 3 months, Essure procedure, or spermicide). For female subjects using a barrier method plus spermicide, that method must be used for at least 14 days prior to Screening.

   Female subjects who are abstinent may participate in the study; however, they must be counseled on the requirement to use appropriate contraception should they become sexually active. This counseling should occur at each study visit and must be documented in source records.
9. Willing and able to understand and provide written informed consent.
10. Willing and able to comply with study requirements and restrictions.
11. Agree to the confidential use and storage of all data and use of all anonymized data for publication including scientific publication.

Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for participation in the study:

1. The following conditions are excluded:
   a) Interstitial lung disease (ILD) known to be caused by domestic and occupational environmental exposures.
   b) Interstitial lung disease (ILD) known to be caused by connective tissue disease.
   c) Interstitial lung disease (ILD) known to be caused by drug related toxicity.

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2. Currently on continuous oxygen therapy for longer than 16 hours at any level or delivered by any modality. Intermittent oxygen use of any duration over any given 24-hour period is allowed.
3. Major psychiatric disorder, which in the opinion of the Investigator, could interfere with the assessment of anti-cough efficacy and/or safety events during the study or with the ability of the subject to cooperate with study requirements.
4. Serum bilirubin > 1.5 × upper limit of normal range at screening unless explained by a clinical diagnosis of Gilbert's syndrome.
5. Serum hepatic alanine aminotransferase or aspartate aminotransferase enzymes > 100 U/L at screening.
6. Estimated glomerular filtration rate ≤ 44 mL/min/1.73 m^2 at screening.
7. Upper or lower respiratory tract infection within 4 weeks of screening.
8. Significant medical condition or other factors that may interfere with the subject's ability to successfully complete the study.
9. History of substance abuse that, as determined by the Investigator, may interfere with the conduct of the study.
10. Known intolerance or hypersensitivity/drug allergy to nalbuphine or vehicle components.
11. Pregnant or lactating female subject.
12. Concurrent enrollment in an ongoing clinical trial or anticipated enrollment in a concurrent clinical trial.
13. Clinical diagnosis of sleep apnea and/or use of continuous positive airway pressure (CPAP).
14. History of clinically significant head injury in past 1 month.
15. Clinical diagnosis of aspiration pneumonitis.
16. Clinical history of opiate withdrawal symptoms following use of opiates.
17. Documented or clinically suspected hypercapnia (pCO_2 >6.0kPa).

Medication-related Exclusions:

18. Known intolerance (gastrointestinal, central nervous system symptoms) or hypersensitivity/drug allergy to opioids.
19. Exposure to any investigational medication, including placebo, within 4 weeks.
20. Potential subjects cannot have received opiates, including opiate-containing anti-cough agents, within 14 days prior to the screening period. Subjects are prohibited from using opioids, including naltrexone, for the duration of the study.
21. Potential subjects cannot currently be receiving benzodiazepines or other CNS Depressant Class Drugs that when used concomitantly with opioids are known to have the potential to cause added pharmacologic effects of depressing CNS activity (See *Section 9.6.2.2* ("Benzodiazepines and Other CNS Depressant Class Drugs").
22. Potential subjects cannot currently be receiving medications that affect serotonergic neurotransmission and that when used concomitantly with opioids can cause serotonin syndrome (See Section *9.6.2.3* ("Serotonergic Class Drugs").
23. Alcohol consumption should be limited for the duration of study treatment (due to the potential cause of added pharmacologic effects of CNS depression when used concomitantly with opioids.
24. Change of IPF-related drug treatment regimen within 8 weeks of screening.

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Cardiac-related Exclusions:

25. Subjects with a history of congestive heart failure of Class 2 or higher as graded using the New York Heart Association (NYHA) classification (*Appendix 8*).
26. Subjects with a history of angina pectoris Grade 2 or higher as graded using the Canadian Cardiovascular Society (CCS) grading scale (*Appendix 7*).
27. History of ventricular tachycardia, Torsade de Pointes, or family history of sudden death.
28. Myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the subject.
29. Serum potassium below the laboratory lower limit of normal.
30. QTcF interval >450 ms (mean of 3 screening ECG QTcF values) if QRS <120 ms (mean of 3 screening ECG QRS values); QTcF interval >480 ms in the presence of Right Bundle Branch Block (RBBB) and/or QRS ≥ 120 ms
31. Heart rate < 45 bpm on any screening measurement. Subjects with a resting heart rate of < 45 bpm will have it repeated once after 5 minutes in the supine position, and if it remains < 45 bpm during the repeat, they will be considered a screen failure.
32. Use of a medication having a "known risk" of Torsade de Pointes (categorized as "KR" on the Credible Meds® website) is not permitted at entry or during the study (See *Appendix 9*).

    Medications associated with a potential risk of QT prolongation, but not clearly associated with Torsade de Pointes, are permitted at study entry if the following criteria are met:

    - Subject has been given medication at stable doses for a full 4 weeks prior to screening.
    - Medication dose will not be increased after screening, or during the study, and it is anticipated that the subject will receive the medication for the entirety of the study.

Test Product, Dose and Mode of Administration:
NAL ER tablets, 27 mg, 54 mg, and placebo tablets BID, orally administered

Reference Therapy, Dose and Duration of Administration:
Matching placebo tablets, orally administered

Duration of Treatment:
Up to 11 weeks

Variables:

Efficacy:

Primary Efficacy Endpoint

- Mean change in daytime cough frequency (coughs per hour) from baseline as assessed by objective digital cough monitoring at Day 22 by treatment. Daytime is defined as the time the subject is awake in the 24 hours after the digital cough monitor is applied for use.

Secondary Efficacy Endpoints

- Relative change in daytime cough frequency (coughs per hour) from baseline at Day 22 (dose: 162 mg BID) by treatment.
- Relative change in 24-hour (combined daytime and nighttime) cough frequency (coughs per hour) from baseline at Day 22 (dose: 162 mg BID) by treatment.

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- Relative change in nighttime cough frequency (coughs per hour) from baseline at Day 22 (dose: 162 mg BID) by treatment.
- Mean change in the E-RS diary cough subscale (E-RS diary question number 2) from baseline at Days 9, 16, and 22 by treatment.
- Mean change in the Cough Severity Numerical Rating Scale at Days 8, 15, and 21 by treatment.
- Mean change in the E-RS diary breathlessness subscale (E-RS diary questions 7, 8, 9, 10, and 11) from baseline at Days 9, 16, and 22 by treatment.
- Mean change in the 14-item EXACT v1.1 e-diary tool total score from baseline at Days 9, 16, and 22 by treatment.
- Mean change in the PROMIS Item Bank v1.0 Fatigue Short Form 7a scale from baseline at Day 21 by treatment.
- Mean change in the CGI-C over time measured at Day 21 by treatment.

Safety: Safety will be assessed based on adverse events, clinical laboratory measurements, locally reviewed and central cardiac core laboratory read ECGs, vital signs, spirometry and physical examinations.

Subjects will also complete the Subjective Opiate Withdrawal Scale (SOWS) on a daily basis via e-diary for 14 days following the last dose of investigational product, whenever that occurs and regardless of the reason (unless consent is withdrawn).

An independent Data Safety Monitoring Board (DSMB) will periodically review safety data.

Pharmacokinetics: Nalbuphine (and/or metabolites) plasma concentration will be measured at Day 21 by treatment group.

Statistical Methods:

Efficacy

The primary efficacy endpoint of percent change in daytime cough frequency (coughs per hour) will be analyzed using a mixed-effects model with sequence, treatment, and time (Day 22) as fixed effects, the baseline value as a covariate, site as a random effect, and subject as a random repeated effect. There will be no imputation for dropouts or missing data for assessments not completed at study visits. A log transformation will be applied to daytime cough frequency; in the presentation of results, log-scale fitted mean treatment group differences at Day 22 will be back-transformed to fitted ratios of geometric means.

As a sensitivity analysis, a negative binomial model will be fitted with the number of coughs at Day 22 as the outcome, with terms for sequence, treatment, and time, as well as baseline cough frequency and subject, and duration of daytime (in hours) as an offset. An autoregressive covariance structure will be assumed for study visits, and the site random effect will use an unstructured covariance matrix.

Secondary efficacy endpoints will be summarized using descriptive statistics. For continuous endpoints (e.g., change from baseline), summaries will include mean, median, standard deviation, minimum, and maximum. For discrete variables (e.g., frequency), summaries will include number of instances and percentage of total instances for that category or time period.

Safety

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The incidence of adverse events will be summarized through the presentation of proportions by Medical Dictionary for Regulatory Activities (MedDRA) body system classification and preferred term. Vital signs and laboratory data will be summarized using descriptive statistics. The extent and duration of use of prohibited or restricted medications will be similarly summarized using descriptive statistics. No formal statistical analysis will be performed on safety outcomes; inferences, if any, will be derived through clinical review and interpretation.

Adverse events of special interest (AESI) that code to the most relevant abuse-related MedDRA preferred terms will be tabulated and descriptive narratives will be written. Additional adverse events that are considered "possibly related to abuse potential" will be tabulated separately.

Electrocardiograms will be reviewed locally and read centrally by specially trained staff, with real-time feedback to clinical sites regarding any findings relevant to safety. Once the database is complete, ECG data (e.g., heart rate, PR, QTcF intervals) will be presented in listings by subject and summarized by collection date and time. A complete ECG assessment will be documented in a separate report from the central ECG laboratory.

Pharmacokinetics

Nalbuphine (parent and/or metabolites) plasma concentration data will be listed by collection time and nalbuphine dose where applicable. Further PK analyses may be conducted if data allow.

Sample Size and Power

The planned sample size of 44 subjects for the final analysis (22 per sequence) provides at least 80% power to detect a 40% reduction in Day 22 daytime cough frequency (coughs per hour) with NAL ER tablet treatment compared to placebo tablets at the 5% significance level (2-sided). This assumes a coefficient of variation (CV) of 1.00 in log-transformed Day 22 cough frequencies. The CV estimated from *Kelsall et al (2011)* data on chronic cough in patients without esophageal catheterization is 1.12; because Kelsall et al data was on 24-hour cough (including nighttime cough, a period of lower coughing rate) and were not taken in a sample of IPF patients only, it is believed that the CV will be lower than in Kelsall et al data.

If the CV is larger than planned at 1.25, this sample size provides > 80% power to detect a 50% reduction from placebo to NAL ER. Alternatively, if the CV is 0.75, this sample size provides > 80% power to detect a 34% reduction from placebo to NAL ER.

Efficacy analyses will be based primarily on the completers population, which consists of all subjects who received both study treatments and completed both treatment periods in the study. However, methods of adjustment for missing or otherwise incomplete data (e.g., failure to complete both treatment periods) will be considered after assessing the extent that such conditions exist at the time of data base lock.

A total of approximately 60 subjects will be randomized to ensure complete data from at least 44 subjects, assuming up to a potential 26% dropout rate.

A statistical update on this Proof-of-Concept (POC) study may be conducted when a minimum of 12 subjects have completed both study periods for the purposes of determining whether POC can be established prior to complete enrollment of the study.

Date of the Protocol:

14 December 2021

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2 SIGNATURE PAGE

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Treatment, Two-Period Crossover Efficacy and Safety Study in Idiopathic Pulmonary Fibrosis with Nalbuphine ER Tablets for the Treatment of Cough

PROTOCOL NUMBER: TR12

Trevi Therapeutics, Inc.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 12/14/2021 | 11:21 AM PST
E2CB85CA625648AD9E23E0AFC0841D17

[redacted] MD

Date (day/month/year)

3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
AE-IPF	acute exacerbations of idiopathic pulmonary fibrosis
AESI	adverse event of special interest
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
ATC	anatomical therapeutic class
BID	twice daily
BMI	body mass index
CGI-C	Clinical Global Impression of Change
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CP	conditional power
CPAP	continuous positive airway pressure
CRA	clinical research associate
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
D	Day
DLco	diffusing capacity of the lung for carbon monoxide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ER	extended release
ERS	European Respiratory Society
E-RS	Evaluating Respiratory Symptoms Scale
EU	European Union
EXACT	EXAcerbation of Chronic pulmonary disease Tool
FDA	Food and Drug Administration of the United States
FVC	forced vital capacity
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
JRS	Japanese Respiratory Society
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	independent ethics committee

ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
IUD	intrauterine contraceptive device
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KR	Known Risk
MedDRA	Medical Dictionary for Regulatory Activities
NIH	National Institutes of Health (US)
NRS	Numerical Rating Scale
OTC	over-the-counter
PK	Pharmacokinetic
POC	proof-of-concept
PPI	proton pump inhibitor
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
QD	once daily
RBBB	Right Bundle Branch Block
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SOWS	Subjective Opiate Withdrawal Scale
TEAE	treatment emergent adverse event
TdP	Torsade de Pointes
UIP	usual interstitial pneumonia
US	United States
WHO	World Health Organization

4 INTRODUCTION

4.1 Background Information on Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is described in an official endorsed ATS/ERS/JRS/ALAT Clinical Practice Guideline (*Raghu et al, 2018*) as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and is defined by the histopathological and/or radiologic pattern of usual interstitial pneumonia (UIP).

Cough and dyspnea are common symptoms of IPF patients with 81% and 90%, respectively, of patients reporting these symptoms at the time of diagnosis. *Swigris et al (2011)* report fatigue as a common, underappreciated, and bothersome symptom of IPF that impacts quality of life but is rarely quantitatively assessed in clinical studies.

Patients participating in the *FDA's "The Voice of the Patient"* stated that cough, shortness of breath, and fatigue had the greatest impact on their daily life. In addition to describing the common day-to-day triggers to their coughing and the impact of coughing on daily living, patients described coughing episodes leading to shortness of breath and exhaustion. Shortness of breath impacted physical activity even after minimal exertion. Fatigue was associated with coughing and also as a result of shortness of breath *("The Voice of the Patient" series report on Idiopathic Pulmonary Fibrosis; page 5-7; March 2015*).

Yorke et al (2014) state that regardless of which health-related quality-of-life instrument has been used in clinical research of IPF patients, the responses are driven by the symptoms of cough, dyspnea, and fatigue, in particular by dyspnea-imposed limitations on physical activities. *Swigris et al (2005)* state that IPF patients report fatigue is as bothersome as breathlessness.

As to the natural history of the disease, while there may be some inter-patient variability as to the rate of disease progression (*Raghu et al, 2011*), IPF has a poor prognosis with median survival of 3.8 years for adults age 65 (*Leder and Martinez, 2018*). Death in the IPF patient is frequently precipitated by an acute respiratory worsening, including the development of "acute exacerbations of IPF" (AE-IPF). The AE-IPF phase is defined as acute worsening of dyspnea and lung function of unknown etiology. It has an annual incidence of up to 20% and is typically associated with median survival of less than 3 months (*Ryerson et al, 2015*).

On physical examination, patients have inspiratory crackles, acrocyanosis, and clubbing. On laboratory workup, most patients have a restrictive pattern on pulmonary function testing, exercise-induced oxygen desaturation, and a chest radiograph with non-specific changes or bilateral reticular abnormalities (*Bjoraker et al, 1998*; *Leder and Martinez, 2018*). The UIP is characterized by chest computed tomography radiologic findings of bilateral reticulation and honey-combing that is predominately peripheral and in the lower lobes and is diagnostic of IPF in the proper clinical setting (*Leder and Martinez, 2018*).

Common comorbidities found in IPF patients include pulmonary hypertension, obstructive sleep apnea, lung cancer, chronic obstructive pulmonary disease (COPD)/emphysema, ischemic heart disease and gastroesophageal reflux disease (GERD) (*Raghu and Richeldi, 2017*). Raghu and

Richeldi (2017) stated that palliative care be offered to IPF patients at all stages of disease management. *Lewis and Scullion (2012)* report that IPF palliative care includes symptom-centered management that encompasses the treatment of cough, dyspnea, and fatigue/deconditioning.

4.2 Background Information on Nalbuphine

Trevi Therapeutics, Inc. (Trevi) has in-licensed an oral pharmaceutical nalbuphine extended-release (ER) tablet product. Nalbuphine is currently only available as a generic medication in an injectable form; no oral formulation of the drug is approved for any medical indication.

The commercially available approved drug product was first marketed in 1979 in the United States (US) as Nubain®, on which the presently sold generic injectable formulations are based. Approved indications in the US include the relief of moderate to severe pain, as a supplement to balanced anesthesia, pre-operative and post-operative analgesia, and obstetrical analgesia during labor and delivery (*US Nalbuphine Package Insert, December 2016*). Nalbuphine remains an unscheduled drug in the US (*Drug Enforcement Agency, 2013*).

Commercial availability in the European Union (EU) of the parenteral formulation of nalbuphine dates to 1986 (*Medicines Evaluation Board in the Netherlands, 2010*) with approved indications for short-term relief of moderate to severe pain and pre- and post-operative analgesia (*UK Nalpain SmPC, January 2011*). Nalbuphine is not listed in the List of Narcotic Drugs Under International Control in accordance with the United Nations Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (*List of Psychotropic Substances Under International Control (2010)*).

Nalbuphine is a member of the "opioid agonist-antagonist" class of drugs with agonistic action at kappa opioid receptors and antagonistic activity at mu opioid receptors (*Yaksh and Wallace 2011)*. The clinical development program of NAL ER tablets has included prior investigational studies for the treatment of prurigo nodularis related pruritus, uremic pruritus in hemodialysis patients as well as safety and efficacy analgesic studies. This study protocol is to investigate NAL ER tablets as a treatment for cough related to IPF. Additional information can be found in the Investigator Brochure.

4.3 Rationale for Investigation of Nalbuphine in Cough and Dyspnea Related to Idiopathic Pulmonary Fibrosis

A detailed briefing document on the rationale for investigating NAL ER tablets in IPF related cough and dyspnea is found in *Appendix 10*. A brief summary is provided below.

There is medical literature reporting that the opioid drug class may be effective antitussives. *Morice et al (2007)* report in chronic cough subjects that morphine is effective treatment. The mixed agonist-antagonist pharmacologic class of drugs has been shown in human studies to have antitussive effect on acute cough during anesthesia induction (*Ai et al 2010; Cheng et al 2016*). The mixed agonist-antagonist butorphanol has been approved as an animal anti-tussive (US *Torbutrol® Package Insert, 2013*).

As it relates to dyspnea from various medical diagnoses, *Jennings et al (2002)* summarized the medical literature on the use of mu agonist opioids in the treatment of dyspnea and supported their continued use in patients with advanced underlying disease, as did *Mahler (2013)*.

The brainstem cough reflex (*Canning 2014*) may be impacted by nalbuphine pharmacological action by lessening the nerve tissue irritability peripherally at the level of the afferent limb of the cough reflex arc by acting directly on receptors on nerve terminals, acting directly at the level of lung tissue where endogenous opioid ligands are likely produced by immune system cells in the parenchymal mileu during the inflammatory and fibrotic processes, or through other pharmacologic actions that reduce peripheral sensitization phenomena in the local inflammatory mileu. In a different disease paradigm, opioid class drugs are known to reduce pain that is mediated via peripheral sensitization induced neuronal signaling.

The physiological phenomena of central sensitization of cough may be occurring in IPF as an explanation of the chronic nature of the cough (*Hope-Gill 2003*). Nalbuphine may be able to act centrally at the brainstem level to desensitize the cough reflex arc and lessen the efferent reflex arc outflow, with the net result that coughing will be lessened or terminated.

Given the density of mu and kappa opiate receptors in the cortex and the anatomical and physiological understanding of the role of cortical activity in dyspnea (*Mahler and O'Donnell 2015*) and cough (*Mazzone et al 2009*), cortical directed pharmacologic action of nalbuphine may also positively impact cough and dyspnea and then lead to less sensation of fatigue. As it relates to dyspnea, nalbuphine pharmacology may act at the perceptual level of modifying the experience of dyspnea that adversely impacts quality of life, as well as pharmacologically modulating central command drives controlling breathing to bring the central nervous system (CNS) respiratory control drives more in balance with the mechanical capacity of ventilator apparatus of the pulmonary organ. Cortical mediated control of cough may be an important regulator of the cough reflex set point that drives frequency and intensity of this reflex action.

5 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of NAL ER tablets in the study population.
- To evaluate the effect of NAL ER tablets on the mean daytime cough frequency (coughs per hour) at Day 22 (dose 162 mg BID) as compared to placebo. Assessment is done using objective digital cough monitoring. Daytime is defined as the time the subject is awake in the 24 hours after the digital cough monitor is applied for use.

5.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the effect of NAL ER tablets on the mean relative change from baseline in daytime cough frequency (coughs per hour) at Day 22 (dose: 162 mg BID).
- To evaluate the effect of NAL ER tablets on the mean relative change from baseline in 24-hour (combined daytime and nighttime) cough frequency (coughs per hour) at Day 22 (dose: 162 mg BID).
- To evaluate the effect of escalating doses of NAL ER tablets on the mean relative change from baseline in nighttime cough frequency (coughs per hour) at and Day 22 (dose: 162 mg BID).
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline on the Evaluating Respiratory Symptoms (E-RS™) diary cough scale (E-RS diary question number 2) by treatment at Days 9, 16, and 22.
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline in the Cough Severity Numerical Rating Scale by treatment at Days 8, 15, and 21.
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline in the E-RS diary breathlessness scale (E-RS diary questions 7, 8, 9, 10, and 11) by treatment at Days 9, 16, and 22.
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline in the 14-item the EXAcerbation of Chronic pulmonary disease Tool (EXACT®) version 1.1 e-diary tool total score by treatment at Days 9, 16, and 22.
- To evaluate the effect of escalating doses of NAL ER tablets on the mean change from baseline in the Patient Reported Outcomes Measurement Information System (PROMIS®) Item Bank v1.0 Fatigue Short Form 7a scale by treatment at Day 21.
- To evaluate the change in the CGI-C over time by treatment measured at Day21.

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is a double-blind, randomized, placebo-controlled, 2-treatment, 2-period crossover efficacy and safety study in IPF subjects with NAL ER tablets for the treatment of cough. The study consists of 2 treatment periods of 3 weeks, each followed by a washout period of 2 weeks.

Treatment Period 1:

During Treatment Period 1, eligible subjects will be randomized (1:1) to one of the following treatment arms:

- **Arm 1:** Active NAL ER tablets followed by crossover Placebo tablets in Treatment Period 2
- **Arm 2:** Placebo tablets followed by crossover NAL ER tablets in Treatment Period 2

Following 3 weeks of dosing in Treatment Period 1, subjects will complete a 2-week washout period before entering Treatment Period 2. Subjects assigned to Arm 1 will receive placebo tablets and subjects assigned to Arm 2 will receive NAL ER tablets during Treatment Period 2. A final 2-week washout period will occur at the completion of Treatment Period 2.

NAL ER Dosing

Subjects on NAL ER tablets will have the dose titrated from 27 mg once daily (QD) to 54 mg BID over a 5-day period and then maintained at 54 mg BID for approximately 4 days. Doses will be subsequently escalated and maintained at 108 mg BID over 1 week and then to 162 mg BID over 6 days.

Study Visits:

Study visits will include screening to determine eligibility, and for each treatment period: visits at Day -1 for baseline assessments, at Days 8, 15, and 21 during treatment, and a follow-up at the end of the 2-week washout period. At study screening and the Day 21 visits, during each treatment period, subjects will have blood drawn for safety analysis. Pharmacokinetic (PK) analysis of nalbuphine plasma concentration will also be done at Day 21. Subjects will complete questionnaires for efficacy evaluations and undergo safety evaluations including an ECG. At the baseline and Day 21 visits, during each treatment period, site staff will place an electronic cough monitor on the subject, which will be worn until the evening of the following day in order to obtain at least a full 24-hour recording period of cough frequency. At the end of each recording session, the monitor will be removed at home by the subject prior to bedtime. Subjects will complete a daily e-diary twice per day.

Subjects who discontinue investigational product, for reasons other than withdrawal of consent, will be considered to have prematurely discontinued treatment and will be asked to complete the premature discontinuation and 2-week off-treatment safety follow-up evaluations.

The schematic of the study design is provided in *Figure 1*.

Figure 1: Study Schematic

D = Day.

6.2 Study Schedule

The schedule of assessments is provided in *Table 1* and *Table 2*.

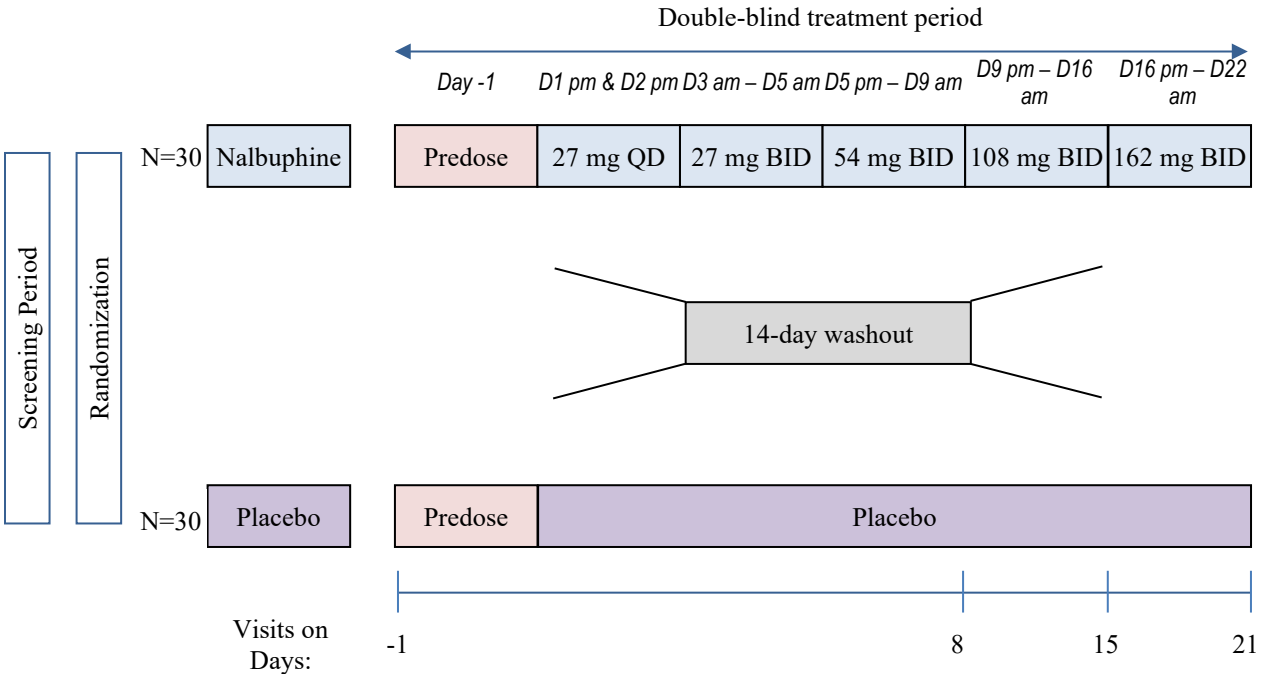

Table 1: Schedule of Events – Screening and Treatment Period 1

		Treatment Period 1[1]							Premature Discontinuation
	Screening	Baseline	Treatment					Follow-up[2]	
Visit:	1	2		3	4	5		6	
	On-Site Visit	On-Site Visit		Phone Visit	Phone Visit	On-Site Visit		On-Site Visit	On-Site Visit
Treatment Day:	-45 to -2	-1	1[3]	8 (+/-1 day)	15 (+/-1day)	21	22[4]	36 (+/-2days)	
Informed consent	X								
Demographics	X								
Medical history	X								
Inclusion/exclusion criteria	X	X							
Height, weight, and BMI	X								
Electrocardiogram (triplicate)[5]	X							X[18]	X
Vital signs[6]	X							X	X
Spirometry[7]	X					X			
DL_{co} measurement[20]	X								
Swallow test	X								
Physical examination	X							X[18]	X
Urine pregnancy test	X	X[8]						X	X
Serum pregnancy test	X								X
Clinical laboratory tests[9]	X					X			X
PK blood sampling						X			
Randomization		X							
Cough monitor – Dispense/train on use		X[10,11]				X[11]			
Cough monitor – Removal/return for downloading of data			X[12]				X[12]		
Cough frequency (via cough monitor)		X	X[12]			X	X[12]		
Cough Severity Numerical Rating Scale	X[13]	X		X	X	X			X
Fatigue Scale (Short Form 7a)		X				X			X
Clinical Global Impression of Change						X			
e-diary – Dispense and train on use		X							
e-diary – Review compliance[19]				X	X	X			
EXACT version 1.1 e-diary tool[14]		<----- Recorded throughout ----->							X
Subjective Opiate Withdrawal Scale e-diary						X[15]			X[15]
Contraceptive counseling (if applicable)	X	X		X	X	X			
Dispense Subject Medication and Symptom Log	X								

		Treatment Period 1[1]							Premature Discontinuation
	Screening	Baseline	Treatment					Follow-up[2]	
Visit:	**1**	**2**		**3**	**4**	**5**		**6**	
	On-Site Visit	**On-Site Visit**		**Phone Visit**	**Phone Visit**	**On-Site Visit**		**On-Site Visit**	**On-Site Visit**
Treatment Day:	**-45 to -2**	**-1**	**1[3]**	**8** (+/-1 day)	**15** (+/-1day)	**21**	**22[4]**	**36** (+/-2days)	
Subject Medication and Symptom Log – Retrieve/review/re-dispense		X		X	X	X			
Record/assess AEs, conmeds, and therapies (including restricted/prohibited medications)[16]	X	X		X	X	X		X	X
Dispense Investigational Product blister card/dosing instructions		X							
Review Investigational Product compliance				X	X				
Retrieve Investigational Product blister card/review compliance/re-dispense						X		X[17]	X[17]
Retrieval of e-diary, medication and symptom log								X	X

BMI = body mass index; PK = pharmacokinetic; AE = adverse event; conmeds = concomitant medications

1 = Investigational product administration in each treatment period will be separated by a washout interval of 2 weeks between dosing.

2 = Follow-up will occur 14±2 days after the last administration of investigational product.

3 = First dose of investigational product for Treatment Period 1 is taken the evening of Day 1 after removal of the cough monitor.

4 = Last dose of investigational product for Treatment Period 1 is the morning dose of Day 22.

5 = Electrocardiogram (ECG) to be recorded prior to blood sampling when possible at scheduled visits where PK and/or clinical labs are obtained. Subjects should be in the supine position for at least 5 minutes prior to obtaining ECGs with all 3 tracings captured within a 3-5 minute window.

6 = Includes heart rate, blood pressure, respiratory rate, body temperature, and pulse oximetry. Vital signs should be taken prior to blood sampling and measured after the subject has been seated for at least 5 minutes.

7 = Performance of spirometry should adhere to ATS/ERS guidelines; required as part of meeting inclusion criterion #2.

8 = A negative urine pregnancy test will be confirmed prior to randomizing any female subjects of childbearing potential.

9 = Blood and urine samples for clinical laboratory testing should be obtained after 8 hours of fasting whenever possible. Clinical chemistry, hematology, urinalysis, and coagulation will be assessed.

10 = Baseline values for the purposes of the statistical analysis of treatment effect on daytime cough frequency during that crossover period. First dose of investigational product on Treatment Day 1 will be taken after removal of the cough monitor.

11 = Monitor will be placed on the subject by site staff at the end of the visit.

12 = Digital cough monitor hookup (24-hour recording); monitor will be worn until the evening of the following day in order to obtain at least a full 24-hour recording period of cough frequency. At the end of each recording session, the monitor will be removed at home by the subject prior to bedtime. On Treatment Day 1, the monitor will be removed prior to taking the first dose of investigational product. Subject to be provided with appropriate shipping material to return monitor for downloading of cough data (after removal).

13 = Administered on paper for screening; required as part of meeting inclusion criterion #6.

14 = E-RS consists of item numbers 1-11 on the 14-item EXACT version 1.1 e-diary tool. E-diary tool will be completed each evening by the subject prior to bedtime. Subject will be reminded to complete this daily at each appropriate study visit.

15 = Subjective Opiate Withdrawal Scale will be completed daily via e-diary for 14 days following discontinuation of investigational product regardless of when this occurs (i.e. Day 23 or premature discontinuation). Site will log into the e-diary portal to confirm subject is completing entries as required during the washout period.

16 = Spontaneous AE reporting will be continuous throughout the study; however, AE assessments will be performed at each visit using non-leading questions.

17 = Retrieve/review compliance at these visits; investigational product and packet will not be re-dispensed.

18 = ECG and physical exam do not need to be repeated at Visit 6 if previously performed for Premature Discontinuation Visit. A brief physical exam may be performed at Visit 6 to document any changes from the previous exam.

19 = During all visits (including those conducted by telephone), site will review e-diary entries for compliance. Site will also retrain the subject on use of e-diary if needed.

20 Subjects without DLco testing in the previous 6 months may be enrolled with medical monitor approval.

Table 2: Schedule of Events – Treatment Period 2

	Treatment Period 2[1]							Premature Discontinuation
	Baseline	Treatment					Follow-up[2]	
Visit:	**6**		**7**	**8**	**9**		**10**	
	On-Site Visit		**Phone Visit**	**Phone Visit**	**On-site Visit**		**On-Site Visit**	
Treatment Day:	**-1**	**1[3]**	**8 (+/-1day)**	**15 (+/-1 day)**	**21**	**22[4]**	**36 (+/-2days)**	
Electrocardiogram (triplicate)[5]							X[17]	X
Vital signs[6]							X	X
Spirometry[7]					X			
Physical examination							X[17]	X
Urine pregnancy test							X	X
Serum pregnancy test	X							X
Clinical laboratory tests[9]	X				X			X
PK blood sampling					X			
Cough monitor – Dispense/train on use	X[10,11]				X[11]			
Cough monitor – Removal/return for downloading of data		X[12]				X[12]		
Cough frequency (via cough monitor)	X	X[12]			X	X[12]		
Cough Severity Numerical Rating Scale	X		X	X	X			X
Fatigue Scale (Short Form 7a)	X				X			X
Clinical Global Impression of Change					X			
e-diary – Re-train on use	X							
e-diary – Review compliance[18]	X		X	X	X			
EXACT version 1.1 e-diary tool[13]	<----- Recorded throughout ----->							X
Subjective Opiate Withdrawal Scale e-diary					X[14]			X[14]
Contraceptive counseling (if applicable)	X		X	X	X			
Dispense Subject Medication Symptom Log	X							
Subject Medication and Symptom Log – retrieve/review/re-dispense			X	X	X			
Record/assess AEs, conmeds, and therapies (including restricted/prohibited medications)[15]	X		X	X	X		X	X
Dispense Investigational Product blister card/dosing instructions	X[8]							
Review Investigational Product compliance			X	X				
Retrieve Investigational Product blister card/ review compliance/re-dispense					X		X[16]	X[16]
Final retrieval of e-diary, medication and symptom log							X	X

PK = pharmacokinetic; AE = adverse event; conmeds = concomitant medications

1 = Investigational product administration in each treatment period will be separated by a washout interval of 2 weeks between dosing.

2 = Follow-up will occur 14±2 days after the last administration of investigational product.

3 = First dose of investigational product for Treatment Period 2 is taken the evening of Day 1 after removal of the cough monitor.

4 = Last dose of investigational product for Treatment Period 2 is the morning dose of Day 22.

5 = Electrocardiogram (ECG) to be recorded prior to blood sampling when possible at scheduled visits where PK and/or clinical labs are obtained. Subjects should be in the supine position for at least 5 minutes prior to obtaining ECGs with all 3 tracings captured within a 3-5 minute window.

6 = Includes heart rate, blood pressure, respiratory rate, body temperature, and pulse oximetry. Vital signs should be taken prior to blood sampling and measured after the subject has been seated for at least 5 minutes.

7 = Performance of spirometry should adhere to ATS/ERS guidelines.

8 = A negative urine pregnancy test will be confirmed prior to randomizing any female subjects of childbearing potential.

9 = Blood and urine samples for clinical laboratory testing should be obtained after 8 hours of fasting whenever possible. Clinical chemistry, hematology, urinalysis, and coagulation will be assessed.

10 = Baseline values for the purposes of the statistical analysis of treatment effect on daytime cough frequency during that crossover period. First dose of investigational product on Treatment Day 1 will be taken after removal of the cough monitor.

11 = Monitor will be placed on the subject by site staff at the end of the visit.

12 = Digital cough monitor hookup (24-hour recording); monitor will be worn until the evening of the following day in order to obtain at least a full 24-hour recording period of cough frequency. At the end of each recording session, the monitor will be removed at home by the subject prior to bedtime. On Treatment Day 1, the monitor will be removed prior to taking the first dose of investigational product. Subject to be provided with appropriate shipping material to return monitor for downloading of cough data (after removal).

13 = E-RS consists of item numbers 1-11 on the 14-item EXACT version 1.1 e-diary tool. E-diary tool will be completed each evening by the subject prior to bedtime. Subject will be reminded to complete this daily at each appropriate study visit.

14 = Subjective Opiate Withdrawal Scale will be completed daily via e-diary for 14 days following discontinuation of investigational product regardless of when this occurs (i.e. Day 23 or premature discontinuation). Site will log into the e-diary portal to confirm subject is completing entries as required during the washout period.

15 = Spontaneous AE reporting will be continuous throughout the study; however, AE assessments will be performed at each visit using non-leading questions.

16 = Retrieve/review compliance at these visits; investigational product and packet will not be re-dispensed.

17 = ECG and physical exam do not need to be repeated at Visit 10 if previously performed for Premature Discontinuation Visit. A brief physical exam may be performed at Visit 10.

18 = During all visits (including those conducted by telephone), site will review e-diary entries for compliance. Site will also retrain the subject on use of e-diary if needed.

6.3 Study Visits and Procedures

For each subject, approximately 10 visits will be performed: screening visit, baseline visits for each treatment period, 2 weekly phone visits plus a Day 21 clinic visit during each treatment period, and an off-treatment safety follow-up visit after each treatment period. The subject will undergo assessments for Follow-Up Visit of Treatment Period 1 and the Baseline Visit for Treatment Period 2 on the same calendar day. The procedures and assessments to be performed during each period/time point are indicated in the Schedule of Events (*Table 1* and *Table 2*). Further relevant details of the evaluations to be performed at each visit are described below.

6.3.1 Treatment Period 1

Screening Visit 1 (Day -45 to Day -2)

Up to 44 days prior to randomization, subjects will participate in a screening visit to determine eligibility to proceed in the study.

Subjects may be re-screened at the discretion of the Medical Monitor and with written permission from the Sponsor. In cases of other unique circumstances that may justify re-screening, Investigators must contact the Medical Monitor to discuss the specific conditions under which subjects may qualify for re-screening.

During screening, subjects will provide informed consent and undergo the following assessments and procedures:

- Review of eligibility/inclusion and exclusion criteria
- Demographics and medical history
- Physical examination
- Height, weight, and body mass index
- ECG (triplicate)
- Measurement of vital signs (blood pressure, heart rate, and respiratory rate), body temperature and pulse oximetry
- Spirometry
- DLco measurement (within the previous 6 months or approval of medical monitor)
- Swallow test
- Cough Severity Numerical Rating Scale (administered on paper at screening)
- Clinical laboratory testing (chemistry, hematology, urinalysis, and coagulation)
- Serum and urine pregnancy testing (females of childbearing potential)
- Contraceptive counseling (if applicable)
- Dispense Subject Medication and Symptom Log

- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

Baseline Visit 2 (Day -1)

Subjects will return for the baseline visit, at which point it will be determined if they meet all study entry criteria prior to being randomized. Subjects will undergo the following assessments during this visit:

- Confirm eligibility against inclusion/exclusion criteria
- Urine pregnancy tests (females of childbearing potential)
- Contraceptive counseling (if applicable)
- Cough Severity Numerical Rating Scale
- Fatigue Scale (Short Form 7a)
- Review and re-dispense Subject Medication and Symptom Log
- Randomization via Interactive Voice/Web Response System (IVRS/IWRS)
- Dispense investigational product blister card
- Provide subject with dosing instructions including instructions for recording daily dosing
- Dispense e-diary and train on its use
- Provide instructions for completing the EXACT version 1.1 e-diary tool
- Dispense cough monitor, train subject on use and provide instruction for removing the device prior to bedtime and prior to taking the first dose of investigational product the next day (Day 1)
- Provide packing and shipping materials for return of cough monitor to Vitalograph® after removal
- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

Telephone Visit 3 and 4 (Day 8 and 15)

Visit 3 (Day 8) and Visit 4 (day 15) will be performed via a telephone call to the Subject. During these visits, subjects will undergo the following assessments:

- Contraceptive counseling (if applicable)
- Cough Severity Numerical Rating Scale
- Review e-diary entries with subjects for compliance, and re-train on use of e-diary if needed
- EXACT version 1.1 e-diary tool and reminder to complete it daily until the next visit
- Review Subject Medication and Symptom Log with subject
- Review blister card accountability/compliance with subject
- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

Treatment Visit 5 (Day 21)

During this visit, subjects will undergo the following assessments:

- Spirometry
- Clinical laboratory testing (chemistry, hematology, urinalysis, and coagulation)
- PK blood sampling
- Contraceptive counseling (if applicable)
- Cough Severity Numerical Rating Scale
- Fatigue Scale (Short Form 7a)
- CGI-C
- Review e-diary entries for compliance, and re-train on use of e-diary if needed
- EXACT version 1.1 e-diary tool and reminder to complete it daily until end of treatment
- Dispense cough monitor, train subject on use and provide instruction for removing the device prior to bedtime the next day (Day 22)
- Provide packing and shipping materials for return of cough monitor to Vitalograph® after removal
- Retrieve, review and re-dispense Subject Medication and Symptom Log
- Collect the investigational product blister card, assess accountability/compliance and return investigational product blister card to subject
- Reminder to take the final dose of investigational product on the morning of the next day (Day 22)
- Instructions for completing the Subjective Opiate Withdrawal Scale (SOWS) daily by e-diary for 14 days (beginning Day 23).
- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

Follow-up Visit 6 (Day 36)

Subjects will return for Follow-up Visit 6 (Day 36) 14 days (+/- 2 days) after the last day of dosing in Treatment Period 1. Subjects will undergo the following assessments:

- Brief physical examination
- ECG (triplicate)
- Measurement of vital signs (blood pressure, heart rate, and respiratory rate), body temperature, and pulse oximetry
- Urine pregnancy test (females of childbearing potential)
- Collect the investigational product blister card and assess accountability/compliance
- Retrieve e-diary
- Retrieve and review Subject Medication and Symptom Log

- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

Before proceeding to Treatment Period 2, females of childbearing potential should have a confirmed negative urine pregnancy test administered by study staff. In most instances, the Baseline visit for Treatment Period 2 will occur on the same calendar day as the Follow-up Visit 6.

6.3.2 Treatment Period 2

Baseline Visit 6 (Day -1)

The Baseline visit for Treatment Period 2 will be completed prior to Day 1 dose administration. Subjects will undergo the following assessments:

- Clinical laboratory testing (chemistry, hematology, urinalysis, and coagulation)
- Serum pregnancy test (females of childbearing potential)
- Contraceptive counseling (if applicable)
- Cough Severity Numerical Rating Scale
- Fatigue Scale (Short Form 7a)
- Re-distribute e-diary to subject, review entries for compliance, and re-train on use
- EXACT version 1.1 e-diary tool and reminder to complete it daily until the next visit
- Dispense cough monitor, re-train subject on use and provide instruction for removing the device prior to bedtime and prior to taking the first dose of investigational product the next day (Day 1)
- Provide packing and shipping materials for return of cough monitor to Vitalograph® after removal
- Dispense investigational product as per IVRS/IWRS
- Provide subject with dosing instructions
- Dispense Subject Medication and Symptom Log
- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

Telephone Visit 7 and 8 (Day 8 and 15)

Visit 7 and 8 (Day 8 and 18) will be performed via a telephone call to subjects. During these visits, subjects will undergo the following assessments:

- Contraceptive counseling (if applicable)
- Cough Severity Numerical Rating Scale
- Review e-diary entries with subject for compliance, and re-train on use of e-diary if needed
- EXACT version 1.1 e-diary tool and reminder to complete it daily until the next visit

- Review Subject Medication and Symptom Log with subject
- Review investigational product accountability/compliance with subject
- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

Treatment Visit 9 (Day 21)

During this visit, subjects will undergo the following assessments:

- Spirometry
- Clinical laboratory testing (chemistry, hematology, urinalysis, and coagulation)
- PK blood sampling
- Contraceptive counseling (if applicable)
- Cough Severity Numerical Rating Scale
- Fatigue Scale (Short Form 7a)
- CGI-C
- Review e-diary entries for compliance, and re-train on use of e-diary if needed
- EXACT version 1.1 e-diary tool and reminder to complete it daily until end of treatment
- Dispense cough monitor, train subject on use and provide instruction for removing the device prior to bedtime the next day (Day 22)
- Provide packing and shipping materials for return of cough monitor to Vitalograph® after removal
- Review and re-dispense Subject Medication and Symptom Log
- Collect investigational product blister card, assess accountability/compliance and return investigational product blister card to subject
- Reminder to take the final dose of investigational product on the morning of the next day (Day 22)
- Instructions for completing the SOWS daily by e-diary for 14 days (beginning Day 23).
- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

Follow-up Visit 10 (Day 36)

Subjects will return for Follow-up Visit 10 (Day 36) 14 days (+/- 2 days) after the last day of dosing in Treatment Period 2. Subjects will undergo the following assessments:

- Brief physical examination
- ECG (triplicate)
- Measurement of vital signs (blood pressure, heart rate, and respiratory rate), body temperature, and pulse oximetry

- Urine pregnancy test (females of childbearing potential)
- Collect investigational product blister card and assess investigational product accountability/compliance.
- Retrieve e-diary
- Retrieve and review Subject Medication and Symptom Log
- Record and assess adverse events, concomitant medications, and therapies (including restricted and prohibited medications)

6.3.3 Premature Discontinuation Visit

Subjects who complete investigational product treatment through the full study treatment course are considered to have completed treatment (even if some doses have been missed). Subjects who discontinue investigational product prior to Treatment Period 2 (Visit 10) will be considered to have prematurely discontinued and will be asked to complete the following visits (unless consent is withdrawn):

- If the decision to discontinue treatment is made during an onsite study visit (scheduled or unscheduled), perform the procedures and assessments outlined in the Premature Discontinuation Visit, regardless of where they are in the study visit schedule.
- If the decision to discontinue treatment is made while the subject is not at a study visit, schedule a visit as soon as possible, but no later than 2 weeks later, to perform the procedures and assessments described in the Premature Discontinuation Visit. Upon notification that the subject has permanently stopped dosing, the site should instruct the subject to begin entering their SOWS data daily via the e-diary.
- The subject should be scheduled to return to the clinic 2 weeks after completion of the Premature Discontinuation Visit for procedures and assessments outlined in the Follow-up Visit (Visit 6 if in Treatment Period 1 and Visit 10 if in Treatment Period 2).

6.3.4 Unscheduled Visits

Should there be a need for an unscheduled visit or assessment (e.g., to manage or follow any unresolved adverse events), the Investigator should use his/her judgment and perform an adequate evaluation of the subject. Vital signs, physical examination, clinical laboratory tests, or any other evaluations required to assess the subject's status should be performed as clinically necessary with data recorded in the Unscheduled Visit section of the electronic Case Report Form (eCRF).

6.4 Rationale for Study Design and Dose Selection

This study has been designed as a Phase 2, double-blind, randomized, placebo-controlled, 2 treatment, 2-period crossover study of NAL ER tablets for the treatment of cough in subjects with IPF. Subjects will receive investigational product for 22 days duration during each period of the crossover. The 2 crossover treatment periods will be separated by a 2-week washout period. The published medical literature including the work of *Bacci et al (2018)* concluded that reduction

in daytime cough frequency may be the most relevant clinical endpoint for assessing the efficacy of drug effect in IPF-related cough. Daytime cough is defined as cough that occurs between the time that the subject wakes up and the time that the subject goes to bed.

The primary study endpoint, mean change in daytime cough frequency (coughs per hour), will be analyzed by use of an objective digital recording device, as consistent with the recommendations of *Boulet et al (2015)* who summarized the CHEST Expert Panel recommendations regarding tools to be used in clinical trials assessing cough. The Panel recommended that acoustic cough counting to assess cough frequency should be done through objective means. Secondarily, as supported by the development work of *Bacci et al (2018)*, the E-RS daily diary will be used as a validated patient-reported outcomes (PRO) instrument in assessing NAL ER tablets efficacy in reducing IPF-related cough.

The patients participating in the *FDA's "The Voice of the Patient" (2015)* reported that in addition to cough, the symptoms of shortness of breath and fatigue had the greatest impact on their daily life. Based on this information, and mechanism of action of NAL ER tablets, these additional symptoms may be amenable to treatment and will be investigated with secondary endpoint metrics.

The *FDA's "The Voice of the Patient" (2015)* mentions that dyspnea is an interchangeable clinical term with breathlessness and describe patients' experience of breathlessness as a symptom, with no distinction in the descriptions being made as to the occurrence of breathlessness with physical activity or breathlessness occurring at rest. The *Bacci et al online supplement (2018)* reports dyspnea in terms of severity of breathlessness with activity and the E-RS breathlessness subscale will be used to analyze whether the concepts of breathlessness associated with or without physical activity can be both or separately affected by NAL ER treatment. The PROMIS fatigue instrument will be used as an additional metric in assessing investigational product efficacy in reducing this burdensome symptom of IPF. There will be an overall clinical assessment of the subject's condition using the Clinical Global Impression of Change instrument.

The study staff, subjects, and Sponsor/clinical research organization (CRO) clinical staff will all be blinded to treatment assignment/sequence to avoid potential bias. Based on titration experience in prior studies in the development program, subjects will have their dose of NAL ER tablets titrated in a blinded manner starting with 27 mg QD up to the target dose of 162 mg BID during the first 2 weeks of active treatment. This titration scheme will increase the likelihood of establishing tolerance to the recognized early side effects of this drug class, mainly in the CNS (dizziness, headache, and somnolence) and gastrointestinal (nausea and vomiting) organ system categories. The target dose of 162 mg BID is within the dose range that was well tolerated in earlier clinical studies of NAL ER tablets.

This study will be conducted in compliance with the protocol and with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

6.5 Safety Monitoring

An independent Data Safety Monitoring Board (DSMB) will periodically review safety data. The frequency of data review and DSMB processes are outlined in the DSMB charter.

Subjects will be closely monitored for safety. AEs will be continuously evaluated throughout the study. Vital signs, locally reviewed and central cardiac core laboratory-read ECGs, physical examinations, spirometry, clinical laboratory testing will be conducted to monitor subject safety.

Although nalbuphine is not a controlled substance in the US or the UK, AEs of special interest (AESIs) that code to the most relevant abuse-related Medical Dictionary for Regulatory Activities (MedDRA) preferred terms will be tabulated and descriptive narratives will be written. Additional AEs that are considered "possibly related to abuse potential" will be tabulated separately (the *FDA's "Assessment of Abuse Potential of Drugs: Guidance for Industry" [2017]*). The list of MedDRA preferred terms for AESIs will be described in the statistical analysis plan (SAP).

Subjects will complete the SOWS on a daily basis for 14 days following the last dose of investigational product. Any subjects who are prematurely discontinued from investigational product will also complete the SOWS daily for the 14 days following the last dose of investigational product (unless consent is withdrawn). The SOWS is a self-administered scale for grading opioid withdrawal symptoms and will be collected via the study issued e-diary.

If subjects experience significant withdrawal symptoms during the 2-week safety observation period, they should contact the Investigator. At the Investigator's discretion, they will be offered treatment.

The most frequently reported AEs from NAL ER Phase 1 and 2 clinical studies were primarily in the nervous system and GI organ system categories, consistent with other opiates. The specific AEs that are considered to be expected with use of NAL ER are nausea, vomiting, somnolence, sedation, dizziness, vertigo, and constipation. These are generally mild or moderate in severity and usually resolve over the titration and early dosing period.

To mitigate opioid-related side effects, NAL ER tablets will be initiated with a titration schedule. Titration is a clinical management strategy consistent with dosing of opioids in general (*Jovey et al 2003*). In this study, the combination of a low starting dosing (27 mg NAL ER on the first day) followed by a relatively slow titration is expected to minimize treatment-limiting opioid adverse effects.

It is known from prior studies, that GI adverse effects (e.g., nausea and vomiting) and CNS adverse effects (e.g., dizziness, somnolence, and headaches) occur early and can be treatment-limiting. In anticipation of the possible occurrence of these effects, pre-medications for these symptoms will be permitted.

In anticipation of the possible occurrence of CNS AEs such as somnolence, subjects will be instructed to be aware of possible CNS AEs that may occur. The evening doses during the titration period should be taken at home. The first dose of any new titration step will occur with an evening dose (see instructions for taking study medication). Subjects will be instructed that the investigational product may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the titration period and in combination with alcohol or tranquilizers or other pharmacologic CNS depressants. Subjects will be instructed not to drive or operate machinery unless they are tolerant to the drug and know how they will react to the medication.

6.6 Risk/Benefit and Ethical Assessment

Nalbuphine has a long history of use in a parenteral formulation, generally for short-term, episodic use related to surgical interventions. The highest dose proposed in the current clinical study is 162 mg BID (324 mg daily dose), well below the highest recommended daily treatment of 144 mg IV dose (equivalent to 864 mg oral dose) for the currently available parenteral administered product. The high peak plasma concentrations that occur in the setting of parenteral use significantly exceed the peak levels observed with NAL ER oral dosing, an observation that is reassuring with respect to the potential for severe, acute toxicity.

Opiate drug class-related concerns such as the potential for physical dependence, linked to long-term use of opiates, is acknowledged. A requirement for completion of a 2-week safety observation period with daily SOWS reporting has been incorporated into the TR12 study. This will facilitate rapid identification and intervention for the respective relevant risks to subjects.

In addition, labeling of opiate-class drugs includes a warning that concomitant use of an opiate together with a benzodiazepine-class drug can increase the risk for respiratory depression, including a risk for respiratory arrest. This warning is based on post-marketing real world data, assessing the experience with a wide range of drugs in these 2 classes and in varied settings including recreational as well as therapeutic usage. In TR12, concomitant benzodiazepine use is not prohibited, and all subjects are informed of this risk through the study Informed Consent Form. At the time of that consent discussion, subjects who are identified as taking a concomitant benzodiazepine should receive the Patient Information Sheet on this topic, as should any subject for whom a concomitant benzodiazepine is subsequently prescribed.

With respect to the published literature addressing respiratory depression with nalbuphine, one relevant study has been identified; which evaluated the respiratory effects of serial intravenous administration of nalbuphine in healthy volunteers. The results were interpreted by the authors as demonstrating a “ceiling” effect for respiratory depression (*Gal et al 1982*). In previous clinical trials with NAL ER, a total of 41 subjects have received concomitant benzodiazepines while receiving NAL ER, and none of these individuals experienced any event of respiratory depression.

In summary, the risk for subjects participating in the TR12 study is judged to be low based on previous experience with oral administration of NAL ER. The current study will utilize a low initiation dose of 27 mg, a gradual dose titration schedule, careful safety monitoring of subjects during the clinical study, and appropriate education of Investigators regarding symptoms of rare but significant AEs linked to the opiate class.

7 SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

7.1 Number of Subjects

Approximately 60 subjects with diagnosed IPF will be enrolled in the study to ensure evaluable data from at least 44 subjects who complete both treatment periods.

7.2 Inclusion Criteria

Subjects eligible for randomization to receive investigational product must meet all the following criteria:

1. Diagnosis of "definite" or "probable" IPF based on ATS/ERS/JRS/ALAT criteria (see *Raghu et al 2018 in Appendix 6*).
2. FVC > 40% predicted of normal.
3. Diffusing capacity of the lung for carbon monoxide corrected for hemoglobin [DL_{CO}] > 25% predicted of normal within the past 6 months. Subjects who have not had DLco testing may be enrolled with medical monitor approval.
4. Chronic cough > 8 weeks.
5. Adequate swallow reflex as assessed by the ability to sip 3 fluid oz (or 89 ml) of water without coughing or choking.
6. Daytime cough severity score ≥ 4 on Cough Severity Numerical Rating Scale at Screening.
7. Males or females age 18 years and older at the time of consent.
8. Females of childbearing potential must use an acceptable method of birth control (if sexually active). All females of childbearing potential must have a negative pregnancy test at the screening and baseline visits.

   For the purpose of this study, all females are considered to be of childbearing potential unless they are postmenopausal (i.e., at least 1 year since last menses and age > 50 years) or surgically sterile (i.e., tubal ligation, hysterectomy, and/or bilateral oophorectomy).

   Sexually active female subjects of childbearing potential are required to use 1 barrier method (e.g., condom, cervical cap, or diaphragm) of contraception in addition to 1 other method (e.g., intrauterine device in place for at least 1-month, stable hormonal contraception for at least 3 months, Essure procedure, or spermicide). For female subjects using a barrier method plus spermicide, that method must be used for at least 14 days prior to Screening.

   Female subjects who are abstinent may participate in the study; however, they must be counseled on the requirement to use appropriate contraception should they become sexually active. This counseling should occur at each study visit and must be documented in source records.
9. Willing and able to understand and provide written informed consent.
10. Willing and able to comply with study requirements and restrictions.
11. Agree to the confidential use and storage of all data and use of all anonymized data for publication including scientific publication.

7.3 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for participation in the study:

1. The following conditions are excluded:
   a) Interstitial lung disease (ILD) known to be caused by domestic and occupational environmental exposures.
   b) Interstitial lung disease (ILD) known to be caused by connective tissue disease.
   c) Interstitial lung disease (ILD) known to be caused by drug related toxicity.
2. Currently on continuous oxygen therapy for longer than 16 hours at any level or delivered by any modality. Intermittent oxygen use of any duration over any given 24-hr period is allowed.
3. Major psychiatric disorder, which in the opinion of the Investigator, could interfere with the assessment of anti-cough efficacy and/or safety events during the study or with the ability of the subject to cooperate with study requirements.
4. Serum bilirubin > 1.5 × upper limit of normal range at screening unless explained by a clinical diagnosis of Gilbert's syndrome.
5. Serum hepatic alanine aminotransferase or aspartate aminotransferase enzymes > 100 U/L at Screening.
6. Estimated glomerular filtration rate ≤ 44 mL/min/1.73 m^2 at Screening.
7. Upper or lower respiratory tract infection within 4 weeks of Screening.
8. Significant medical condition or other factors that may interfere with the subject's ability to successfully complete the study.
9. History of substance abuse that, as determined by the Investigator, may interfere with the conduct of the study.
10. Known intolerance or hypersensitivity/drug allergy to nalbuphine or vehicle components.
11. Pregnant or lactating female subject.
12. Concurrent enrollment in an ongoing clinical trial or anticipated enrollment in a concurrent clinical trial.
13. Clinical diagnosis of sleep apnea and/or use of CPAP.
14. History of clinically significant head injury in past 1 month.
15. Clinical diagnosis of aspiration pneumonitis.
16. Clinical history of opiate withdrawal symptoms following use of opiates.
17. Documented or clinically suspected hypercapnia (pCO_2 > 6.0kPa).

Medication-related Exclusions:

18. Known intolerance (gastrointestinal, central nervous system symptoms) or hypersensitivity/ drug allergy to opioids.

19. Exposure to any investigational medication, including placebo, within 4 weeks.
20. Potential subjects cannot have received opiates, including opiate-containing anti-cough agents, within 14 days prior to the screening period. Subjects are prohibited from using opioids, including naltrexone, for the duration of the study.
21. Potential subjects cannot currently be receiving benzodiazepines or other CNS Depressant Class Drugs that when used concomitantly with opioids are known to have the potential to cause added pharmacologic effects of depressing CNS activity (See Section *9.6.2.2* ("Benzodiazepines and Other CNS Depressant Class Drugs").
22. Potential subjects cannot currently be receiving medications that affect serotonergic neurotransmission and that when used concomitantly with opioids can cause serotonin syndrome (See Section *9.6.2.3* ("Serotonergic Class Drugs").
23. Alcohol consumption should be limited for the duration of study treatment (due to the potential cause of added pharmacologic effects of CNS depression when used concomitantly with opioids.
24. Change of IPF-related drug treatment regimen within 8 weeks of Screening.

Cardiac-related Exclusions:

25. Subjects with a history of congestive heart failure of Class 2 or higher as graded using the New York Heart Association classification (*Appendix 8*).
26. Subjects with a history of angina pectoris Grade 2 or higher as graded using the Canadian Cardiovascular Society grading scale (*Appendix 7*).
27. History of ventricular tachycardia, Torsade de Pointes, or family history of sudden death.
28. Myocardial infarction or acute coronary syndrome within the previous 3 months, as reported by the subject.
29. Serum potassium below the laboratory lower limit of normal.
30. QTcF interval >450 ms (mean of 3 screening ECG QTcF values) if QRS <120 ms (mean of 3 screening ECG QRS values); QTcF interval >480 ms in the presence of Right Bundle Branch Block (RBBB) and/or QRS $\geq$ 120 ms
31. Heart rate < 45 bpm on any screening measurement. Subjects with a resting heart rate of < 45 bpm will have it repeated once after 5 minutes in the supine position, and if it remains < 45 bpm during the repeat, they will be considered a screen failure.
32. Use of a medication having a "known risk" of Torsade de Pointes (categorized as "KR" on the Credible Meds® website) is not permitted at entry or during the study (See *Appendix 9*).

    Medications associated with a potential risk of QT prolongation, but not clearly associated with Torsade de Pointes, are permitted at study entry if the following criteria are met:

    - Subject has been given medication at stable doses for a full 4 weeks prior to Screening.
    - Medication dose will not be increased after screening, or during the study, and it is anticipated that the subject will receive the medication for the entirety of the study.

7.4 Withdrawal Criteria

Subjects have the right to withdraw from the study at any time for any reason, without prejudice. At any point, the Investigator may discontinue the subject's study participation at his/her discretion and ensure the subject receives appropriate medical care. The Investigator may consult the Medical Monitor to discuss out-of-range test results. The subject may also be withdrawn at the request of the Sponsor. Additionally, although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time and for any reason.

Subjects will be withdrawn from the study for any of the following reasons:

- There is deterioration in the subject's signs and symptoms and/or the subject develops a disease or condition that, in the opinion of the Investigator, would compromise the subject's safety by continuing in the study.
- In the Investigator's judgment, it is in the best interest of the subject.
- There is a violation of the protocol inclusion and/or exclusion criteria, as deemed relevant by the Investigator and discussed with the Medical Monitor.
- The subject withdraws consent for study participation.
- Sponsor terminates the study for any reason.
- Develops a QTcF > 500 ms (mean of 3 ECG QTcF values) in subjects who were randomized without ECG findings of RBBB and/or QRS ≥ 120 ms.
- Develops QTcF > 530 ms (mean of 3 ECG QTcF values) in subjects who were randomized with ECG findings of RBBB and/or QRS ≥ 120 ms.
- Increase from QTcF baseline of > 60 ms (mean determination from 3 ECG values)
- Death of the subject.

If a subject withdraws prematurely from the study during a treatment period due to any of the above criteria or any other reason (unless consent is withdrawn), study staff should make every effort (at withdrawal) to have the subject complete as many of the safety assessments including the SOWS, if possible. The reason for subject withdrawal must be documented in the eCRF. Subjects who withdraw from the study will not be replaced.

If a subject is lost to follow-up, attempts to contact the subject must be made and documented in the subject's eCRF.

If the Sponsor decides to terminate the study, the reason(s) for termination will be documented in the source documents and eCRFs.

7.5 Premature Discontinuation of Investigational Product Treatment

Subjects who discontinue investigational product, for reasons other than withdrawal of consent, will be considered to have prematurely discontinued treatment and will be asked to complete the premature discontinuation and 2-week off-treatment safety follow-up evaluations.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Endpoints

8.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in daytime cough frequency (coughs per hour) from baseline as assessed by objective digital cough monitoring at Day 22 by treatment. Daytime is defined as the time the subject is awake in the 24 hours after the digital cough monitor is applied for use.

8.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Relative change in daytime cough frequency (coughs per hour) from baseline at Day 22 (dose: 162 mg BID) by treatment.
- Relative change in 24-hour (combined daytime and nighttime) cough frequency (coughs per hour) from baseline at Day 22 (dose: 162 mg BID) by treatment.
- Relative change in nighttime cough frequency (coughs per hour) from baseline at Day 22 (dose: 162 mg BID) by treatment.
- Mean change in the E-RS diary cough subscale (E-RS diary question number 2) from baseline, at Days 9, 16, and 22 by treatment.
- Mean change in the Cough Severity Numerical Rating Scale at Days 8, 15, and 21 by treatment.
- Mean change in the E-RS diary breathlessness subscale (E-RS diary questions 7, 8, 9, 10, and 11) from baseline at Days 9, 16, and 22 by treatment.
- Mean change in the 14-item EXACT v1.1 e-diary tool total score from baseline at Days 9, 16, and 22 by treatment.
- Mean change in the PROMIS Item Bank v1.0 Fatigue Short Form 7a scale from baseline at Day 21 by treatment.
- Mean change in the CGI-C over time measured at Day21 by treatment.

8.2 Efficacy Assessments

Efficacy assessments during each of the 2 treatment periods will include 24-hour digital cough monitoring of cough frequency, a daily e-diary tool, and instruments of patient-reported outcomes.

8.2.1 Digital Cough Monitor

Boulet et al (2015) summarized the CHEST Expert Panel recommendations regarding tools to be used in clinical trials assessing cough. The Panel recommended acoustic cough counting to assess cough frequency should be done through objective means.

Measurement of cough frequency will be done using objective digital cough monitoring. The digital cough monitor consists of a portable sound recording device, which is worn in a pouch or pocket. The small microphone is clipped onto the subject's collar or lapel, as close as possible to the anterior neck. A continuous sound recording is made for up to 36 hours. The digital recording is then processed through accompanying computer software, which automatically registers sound patterns typical for cough. Software output provides the total number of cough events over the entire time period of recording and average hourly cough frequency.

At the baseline visit for each treatment period (the day prior to investigational product initiation), and at subsequent treatment visits, site staff will place the digital cough monitor on the subject prior to their departure from the clinic. The monitor will be worn until the evening of the following day in order to obtain at least a full 24-hour recording period of cough frequency. At the end of each recording session, the monitor will be removed at home by the subject prior to bedtime. On Day 1 of each treatment period, the monitor will be removed prior to taking the first dose of investigational product.

8.2.2 Subject e-Diary

All subjects randomized into the study will be provided with a device with an application for a subject e-diary, along with instructions for its use. The device will be password protected. Subjects will complete daily e-diaries, including compliance with investigational product dosing, and answer study specific questionnaires throughout the duration of the study.

Queries will be handled by the vendor managing the e-diary data through the clinical site. The e-diary data will be reviewed by the study staff. The subject will return the e-diary to the site at the follow-up visit of Treatment Period 2 or discontinuation visit.

8.2.3 EXACT 14-item e-Diary Tool and E-RS Diary Cough and Breathlessness Scales

The EXACT is a 14-item daily diary tool PRO instrument that was originally developed to quantify and measure exacerbations of COPD. The E-RS daily diary is a derivative instrument of the EXACT that consists of the 11 respiratory symptoms items contained within the 14-item EXACT that measures the effect of treatment on the severity of respiratory symptoms. Since the E-RS is not administered separately from the EXACT, both a total 14--item EXACT total score will be computed as a secondary efficacy endpoint and a separate analysis of the E-RS 11-items will be done based on the methodology reported in Bacci et al (2018).

Bacci et al (2018) reported on the use of the E-RS daily diary specifically in IPF patients. The authors concluded that analyzing the E-RS daily diary instrument into four separate respiratory symptom domain scales (with no total E-RS score computed) is a valid, reliable and sensitive measure of four distinct respiratory symptoms.

The four domain scales are breathlessness (E-RS items 7, 8, 9, 10, and 11; score range, 0-23), cough (E-RS item 2; score range 0-4), sputum (E-RS items 3 and 4; score range, 0-8), and chest symptoms (E-RS items 1, 5, and 6; score range 0-12). A higher score on the scale indicates a more severe grade to the symptom. The cough and breathlessness symptom domain scale scores will each be studied as secondary efficacy endpoints in this study.

A copy of the daily diary tool EXACT version 1.1 is provided in *Appendix 1*. Subjects will complete the EXACT scale via the study specific e-diary.

8.2.4 Cough Severity Numerical Rating Scale

The Cough Severity Numerical Rating Scale instrument (*Boulet et al 2015*) is a single-dimension 11-point Likert scale ranging from zero ("no cough") to 10 ("worst possible cough"). In addition to its use as a screening instrument, change in the Cough Severity Numerical Rating Scale over the conduct of the study will be monitored as a secondary efficacy endpoint.

A copy of the Cough Severity Numerical Rating Scale is provided in *Appendix 2*. The scale will be administered on paper during the Screening Visit. Once a subject is randomized, the scale will be administered via the study specific e-diary.

8.2.5 PROMIS Item Bank v1.0 Fatigue Short Form 7a Scale

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a US National Institutes of Health (NIH) funded initiative to develop and validate patient reported outcomes (PROs) for clinical research and practice.

The PROMIS fatigue scales were developed to assess a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. The short form versions are universal rather than disease specific (See *PROMIS Fatigue Scoring Manual*).

The PROMIS Fatigue Short Form 7a is a self-administered Likert-type rating 5-point scale of 7 questions that assess tiredness, exhaustion, energy, fatigue limit, tiredness to think, tiredness impact on hygiene and impact on ability to exercise strenuously over the past 7 days.

The PROMIS Fatigue Short Form 7a is provided in *Appendix 3*. This scale will be administered via the study specific e-diary during onsite visits.

8.2.6 Clinical Global Impression of Change Scale

The CGI-C was initially developed for use to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning after initiating a study medication (*Guy 1976*) and is now widely used as an instrument in clinical trials with CNS acting medications (*Busner et al 2007*). The CGI-C provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.

The CGI-C is a one-item measure evaluating change from the initiation of treatment on a seven-point scale. Subsequent to a clinical evaluation, the CGI-C form can be completed in less than a minute by an experienced rater. In practice, the CGI-C captures clinical impressions that transcend mere symptom checklists. The CGI-C can track clinical progress across time.

The CGI-C will be administered during the Day 21 visits of each treatment period. The CGI-C is provided in *Appendix 5*.

8.3 Pharmacokinetic Assessments

To determine the plasma concentration of nalbuphine and metabolites, blood samples will be collected at the Day 21 visits of each treatment period.

8.4 Safety Assessments

Safety will be assessed based on adverse events, clinical laboratory measurements, locally reviewed and central cardiac core laboratory read ECGs, vital signs, spirometry and physical examinations.

Subjects will also complete the SOWS on a daily basis for the 14 days following the last dose of investigational product, whenever that occurs and regardless of the reason (unless consent is withdrawn).

An independent Data Safety Monitoring Board will periodically review safety data.

8.4.1 Adverse Events

The Investigator will determine during the course of the study whether any adverse events have occurred. Subjects will be questioned in a general way, and no specific symptoms will be suggested. *Section 10* contains additional information with regard to adverse event reporting.

8.4.2 Clinical Laboratory Tests

Clinical laboratory tests will be performed by a qualified central laboratory. Whenever possible, blood samples are to be obtained after the collection of vital signs and ECG recordings at designated visits. Clinical laboratory samples should be obtained following an overnight fast (minimum of 8 hours) unless contraindicated due to medication, dietary, or clinical restrictions. If the sample was obtained with less than 8 hours of fasting, the source documents and the lab requisition should be marked to indicate that the sample was obtained under non-fasting conditions. Blood samples will be collected and processed as indicated in the central laboratory manual.

The following clinical laboratory analytes will be measured:

Hematology:	Hematocrit, hemoglobin, red blood cell count, white blood cell count, differentials (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, and reticulocytes
Serum chemistry:	Albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, carbon dioxide, creatinine, total bilirubin, gamma-glutamyl transferase, glucose, lactic

	dehydrogenase, phosphorus, potassium, sodium, total cholesterol, total protein, and uric acid
Urinalysis:	Color, specific gravity, pH, glucose, ketones, protein, bilirubin, urobilinogen, blood, and microscopy (only on urine samples with abnormal urinalysis results)
Coagulation:	Prothrombin time, international normalized ratio, and activated partial thromboplastin time

8.4.3 Pregnancy Tests

Urine and serum pregnancy tests will be performed as specified in the Schedule of Events for females of childbearing potential regardless of sexual activity status or method of contraception. The subject must have a confirmed negative test prior to randomization. In addition, during Follow-up Visit 6 (Treatment Period 1), the urine pregnancy test must be negative prior to providing the subjects will their next supply of study medication.

8.4.4 Vital Signs

Vital signs (blood pressure, heart rate, and respiratory rate), body temperature and pulse oximetry will be measured, prior to blood sampling whenever possible, according to the Schedule of Events (*Table 1* and *Table 2*). Blood pressure will be measured with a standard mercury sphygmomanometer or an automated oscillometric blood pressure monitor after the subject has been in a sitting position for at least 5 minutes.

8.4.5 Physical Examination

A physical examination will be performed at the screening visit and subsequently according to the Schedule of Events (*Table 1* and *Table 2*). This evaluation will include examination of the following body systems: general appearance, eyes, ears, nose, throat, head and neck, chest and lungs, cardiovascular, abdomen, musculoskeletal, lymphatic, dermatological, neurological, and extremities. A brief physical exam may be performed at Visit 6 (Treatment Period 1) and Visit 10 (Treatment Period 2) in order to document any changes present since the previous exam.

8.4.6 Electrocardiogram Assessments

ECGs are to be performed in triplicate after the subject has been in the supine position for at least 5 minutes with all 3 tracings obtained within a period of 3-5 minutes. Whenever possible, ECG testing should be performed prior to the collection of vital signs and blood samples (clinical laboratory and PK samples).

A standard ECG will be obtained according to the Schedule of Events (*Table 1* and *Table 2*) and recorded prior to blood sampling. Electrocardiograms will be reviewed locally for safety by the Investigator and/or their designee. The ECGs will be read centrally for the purpose of meeting the ECG study inclusion criteria, study withdrawal criteria and ECG intervals (PR, RR, QRS, QT, and

QTcF using nomogram table), rate, rhythm, and other clinically significant abnormalities (e.g., left ventricular hypertrophy, pathological Q-waves).

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8.4.7 Spirometry

Spirometry will be used to assess FVC in order to exclude subject candidates with severe pulmonary ventilation (FVC > 40% predicted of normal required to meet inclusion criteria). Spirometry will also be used during the course of the study as a safety measure to objectively assess pulmonary breathing mechanics. Performance of spirometry should adhere to ATS/ERS guidelines with reference to predicted equations (predicted values) used locally at the site.

8.4.8 DLco

Diffusing capacity of the lung for carbon monoxide testing, performed within the past 6 months, will be used to assess lung function. Potential subjects with test results indicative of severe gas exchange mechanics should be excluded from the study. Subjects who have not had DLco testing within the previous 6 months may be enrolled with medical monitor approval.

8.4.9 Swallow Test

Subjects will be asked to drink 3 fluid oz (or 89 ml) of water uninterrupted and will be evaluated by clinical staff for their ability to swallow during and up to one minute after the completion of the test. This test will be used as a screening assessment to verify adequate swallow reflex and may be repeated, if necessary.

8.4.10 Subjective Opiate Withdrawal Scale

Subjects will complete the SOWS on a daily basis for 14 days following the last dose of investigational product in each treatment period. Any subject discontinued from investigational product, prior to completion of the study, will also complete the SOWS daily for the 14 days following the last dose of investigational product (unless consent is withdrawn). The SOWS is a self-administered scale for grading opioid withdrawal symptoms.

The SOWS is provided in *Appendix 4*. Subjects will complete the SOWS via the study specific e-diary.

9 STUDY CONDUCT

9.1 Treatments Administered

The investigational product in this trial is NAL ER tablets or matching placebo tablets. The NAL ER tablets are round, white to off-white, film-coated tablets containing either 27 or 54 mg of nalbuphine (equivalent to approximately 30 or 60 mg nalbuphine HCl); The 27 and 54 mg NAL ER round tablets are identical in appearance. The matching placebo tablet supplied is identical in appearance to the 27 and 54 mg tablets.

Following randomization, the subject will be dispensed a blister card containing 22 days of dosing for Treatment Period 1. Dosing will consist of 3 tablets for the AM dose and 3 tablets for the PM dose. In Treatment period 1, subjects assigned to Arm 1 will receive a combination of 27 mg/54 mg/placebo tablets, and subjects assigned to Arm 2 will receive placebo tablets only. Note: There will be no tablets in the blister card for Days 1 and 2 AM and Day 22 PM. Upon completion of Treatment Period 1 and the 2-week washout period, subjects will be provided with the appropriate cross over treatment for Treatment Period 2. For example, subjects in Arm 1, receiving a combination of 27 mg/54 mg/placebo tablets in Treatment Period 1, will receive placebo tablets in Treatment Period 2. Subjects in Arm 2, receiving placebo tablets only in Treatment Period 1, will receive a combination of 27 mg/54 mg/placebo tablets in Treatment Period 2. The cross over treatments will all be double-blinded.

For subjects assigned to NAL ER treatment, the dose will be titrated from a starting dose of 27 mg QD to the target dose of 162 mg BID over the first 2 weeks of the double-blind treatment period and maintained at 162 mg BID during the third week of the treatment period. The dosing scheme is shown in *Table 3*.

Table 3: Dosing Scheme

Treatment Period	Visit No.	Treatment Day	Dose (mg)			
			Arm 1		Arm 2	
			AM	PM	AM	PM
Treatment Period 1	2	-1	—	—	—	—
		1	—	27	—	Placebo
		2	—	27	—	Placebo
		3	27	27	Placebo	Placebo
		4	27	27	Placebo	Placebo
		5	27	54	Placebo	Placebo
		6	54	54	Placebo	Placebo
		7	54	54	Placebo	Placebo
	3	8	54	54	Placebo	Placebo
		9	54	108	Placebo	Placebo
		10	108	108	Placebo	Placebo
		11	108	108	Placebo	Placebo
		12	108	108	Placebo	Placebo
		13	108	108	Placebo	Placebo
		14	108	108	Placebo	Placebo
	4	15	108	108	Placebo	Placebo
		16	108	162	Placebo	Placebo
		17	162	162	Placebo	Placebo
		18	162	162	Placebo	Placebo
		19	162	162	Placebo	Placebo
		20	162	162	Placebo	Placebo
	5	21	162	162	Placebo	Placebo
		22	162	—	Placebo	—
2-Week Washout						
Treatment Period 2	6	-1	—	—	—	—
		1	—	Placebo	—	27
		2	—	Placebo	—	27
		3	Placebo	Placebo	27	27
		4	Placebo	Placebo	27	27
		5	Placebo	Placebo	27	54
		6	Placebo	Placebo	54	54
		7	Placebo	Placebo	54	54
	7	8	Placebo	Placebo	54	54
		9	Placebo	Placebo	54	108
		10	Placebo	Placebo	108	108
		11	Placebo	Placebo	108	108
		12	Placebo	Placebo	108	108
		13	Placebo	Placebo	108	108
		14	Placebo	Placebo	108	108
	8	15	Placebo	Placebo	108	108
		16	Placebo	Placebo	108	162
		17	Placebo	Placebo	162	162
		18	Placebo	Placebo	162	162
		19	Placebo	Placebo	162	162
		20	Placebo	Placebo	162	162
	9	21	Placebo	Placebo	162	162
		22	Placebo	—	162	—
2-Week Washout						

Investigational product can be taken with or without food. Tablets must be swallowed whole without crushing or chewing. Subjects will be instructed to take the AM and PM investigational product tablets at the same times of the day, approximately 12 hours apart, preferably with at least 240 mL (approximately 8 ounces) of water. If the subject does not take a particular dose at the planned time, he or she may take it within ± 2 hours.

Subjects will confirm whether or not they took their dose(s) and the dosing time for both the AM and the PM dose. Any discrepancies between the dosing records and the number of actual versus expected tablets returned to the site, should be documented at the actual visit in which the investigational product is returned for investigational product drug accountability and investigational product compliance assessments.

Multiple Missed Doses

If the subject misses 3 (or more) consecutive doses, please contact the study Medical Monitor for dosing instructions. In no case should subjects take additional doses of investigational product to make up for missed doses. If investigational product is being restarted after missed doses, the subject should be instructed not to remove the tablets from the days and/or time points on which investigational product was missed; these tablets are to remain in the blister card. The subject is to be instructed on when to resume taking investigational product.

9.2 Study Treatment Packaging and Labeling

Please see the pharmacy manual for additional information on investigational product supplies, packaging, storage, dispensation, and accountability.

9.2.1 Labeling

Blister cards will be labeled with, at minimum: contents, storage conditions, expiration date, clinical trial statement, and the name of the sponsor (Trevi Therapeutics, Inc).

9.2.2 Storage

NAL ER tablets and placebo tablets should be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F to 86°F). The investigational product should be stored away from any extreme conditions of temperature, light, or humidity as an additional precaution.

9.2.3 Blinding and Randomization of Study Treatments

Randomization will be performed via IVRS/IWRS. Upon confirmation of eligibility by the study site and completion of all scheduled procedures at the Baseline (Day -1) visit, subjects will be randomized in a 1:1 ratio to either NAL ER tablets or placebo tablets for Treatment Period 1. Subjects will take the converse study treatment during Treatment Period 2 (the second crossover period).

9.3 Procedure for Breaking the Randomization Code

Under normal circumstances, the blind will not be broken. In the event of a medical emergency, when management of a subject's condition requires knowledge of the treatment assignment, the blind may be broken via the IVRS/IWRS.

Reasons for unblinding will be documented in the eCRF. The date and the identity of the person responsible for breaking the blind must be also documented.

9.4 Subject Compliance

Drug compliance is a critical data observation in all clinical trials and is assessed through the drug accountability records. Returned blister cards will be compared to subject dosing information to assess compliance at each study visit. An accurate and current accounting of the dispensing and return of investigational product for each subject will be maintained on an ongoing basis by a member of the study site staff. The amount of investigational product dispensed and returned by the subject will be recorded on the appropriate investigational product accountability forms at each visit.

Compliance is defined as the amount of investigational product that should have been taken by a subject based on the dosing instructions provided during the period for which investigational product was dispensed. This is typically expressed as percent (%) compliance and is calculated based on the number of tablets actually taken in a particular time interval divided by the number of tablets that should have been taken or prescribed for that time interval. Compliance will be documented after each investigational product return, based on the information on the investigational product accountability forms.

Any dosing and/or compliance discrepancies will be noted in source documents for the applicable subject visit.

9.5 Investigational Product Accountability

The Investigator must ensure that all investigational product supplies are kept in a secure locked area, under controlled temperature, with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all investigational product shipped by the Sponsor or the Sponsor's representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all investigational product.

9.6 Concomitant and Prohibited Medications

9.6.1 Concomitant Medications

Subjects may receive all clinically indicated medications during the study with the exceptions noted in *Section 9.6.2 Prohibited Medications* and *Appendix 9*.

Any medication taken by a subject within the 14 days prior to the screening period, and during the course of the study, will be recorded on the eCRF along with the reason for use. During the study,

each subject will be instructed to report the use of all medication, including over-the-counter (OTC) medications, herbal medications, vitamins, and nutritional supplements on the study specific medication log. Sites should instruct subjects to bring the log to each study visit for review. Subjects will also be instructed about the importance of not taking any new medications during the study (including OTC medications) without consulting the Investigator. After screening, if the subject begins taking prohibited or restricted medications, they are to be recorded on the corresponding Concomitant Medication eCRF.

9.6.2 Prohibited Medications

Use of all other investigational products is prohibited during the study. A subject who initiates an investigational product during the study should be discontinued.

Subjects are to be washed out of any medications meeting exclusion criteria for at least the minimal time periods indicated in the protocol

9.6.2.1 Use of Other Opioid Medications

Subjects cannot have used opiate drugs, including opiate containing anti-cough agents for 14 days prior to the screening period of the study. Subjects are prohibited from using opioids, including naltrexone, for the duration of the study. Use of acetaminophen, non-steroidal anti-inflammatory medications, and aspirin is permitted.

Concomitant use of opioid antagonists (e.g., naloxone, naltrexone) is also prohibited during the study, unless required for urgent reversal of opioid adverse effects or opioid overdose.

9.6.2.2 Benzodiazepines and Other CNS Depressant Class Drugs

Because of the potential for an opioid class drug to cause respiratory depression when used concomitantly with other drug classes known to be CNS depressants, the following types of medications are prohibited during the course of the study: sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, general anesthetics and antipsychotics. Alcohol is a known CNS depressant and its use should be limited during the course of the study. Please refer to the "Risk from Concomitant Use with Benzodiazepines or Other CNS Depressants" section of the United States Nalbuphine HCl Package Insert (Nalbuphine HCl for injection, for intramuscular, subcutaneous or intravenous use (2016)) for additional information.

9.6.2.3 Serotonergic Class Drugs

Because of the rare but potentially life-threatening condition of serotonin syndrome that can result from the concomitant administration of serotonergic drugs, medications that may induce this syndrome are prohibited during the course of the study. Drug classes to be prohibited are: serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists and monoamine oxidase inhibitors (MAOIs), tetracyclic antidepressants (i.e. mirtazapine) and 5-HT2 antagonists (i.e. trazadone). Other drugs to be excluded are: tramadol, which has mechanistic interactions as both an opioid mu-receptor agonist and serotonin reuptake inhibition, the antibiotic linezolid (an oxazolidinone organic compound with monoamine oxidase inhibitory activity) and intravenous drug methylene

blue (methylthioninium chloride) which is mechanistically a potent monoamine oxidase inhibitor. Please refer to the "Drug Interactions" section of the United States Nalbuphine HCl Package Insert (Nalbuphine HCl for injection for intramuscular, subcutaneous or intravenous use (2016)) for additional information.

9.6.2.4 Prohibited Medications Related to Risk of Torsades de Pointes

Subject are not to receive a medication that is classified as having a known risk for Torsade de Pointes (see *Appendix 9*, for cardiovascular related prohibited medications with a known risk of Torsade de Pointes, classified as "KR").

9.6.3 Symptom Management

Nalbuphine use may be associated with nausea, headache and dizziness upon initiation of treatment and during titration. The literature on managing opiate initiation generally recommends against prophylactic use, as only about 1 in 5 subjects will experience nausea. However, at the Investigator's discretion, anti-emetics that are NOT classified as having a known risk for Torsade de Pointes (see *Appendix 9*, for cardiovascular related prohibited medications with known risk of TdP classified as known risk "KR") may be prescribed at the baseline visit, in which case the subject should be educated on the appropriate, as needed use, of early treatment of symptoms. Headaches and dizziness can also be treated with agents commonly prescribed for these symptoms (e.g., acetaminophen for headache and scopolamine patch for dizziness) during the titration period, but these symptoms are less frequent and usually do not warrant prophylaxis.

9.7 Termination of the Study

If, in the opinion of the Investigator, the clinical observations in the study suggest that it may be unwise to continue, the Investigator may terminate the study after consultation with the Sponsor. A written statement fully documenting the reasons for such a termination will be provided to the Sponsor. In addition, the Sponsor may terminate the study at any time. Furthermore, if it becomes apparent that subject enrollment is unsatisfactory with respect to quality or quantity or that data recording is inaccurate or incomplete on a chronic basis, the Sponsor has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the Investigator, the Institutional Review Board (IRB) / Independent Ethics Committee (IEC), and regulatory authorities, if required. In the event a serious adverse event (SAE) is part of the reason for early termination of the study, all documentation relating to the event(s) must be obtained and filed appropriately.

10 ASSESSMENT OF SAFETY

10.1 Adverse Event Definition

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation subject reported on or after the first screening date. A Treatment Emergent Adverse Event (TEAE) is any untoward medical occurrence in a clinical investigation subject or subject administered a pharmaceutical product on or after the initial administration of investigational product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom whether or not related to the medicinal (investigational) product, or disease temporally associated with the use of a medicinal (investigational) product.

The AE may be any of the following:

- A new illness
- Worsening of a pre-existing condition
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the investigational product, including comparator
- A combination of 2 or more of these factors

No causal relationship with the investigational product or with the clinical study itself is implied by the use of the term "AE."

Surgical procedures themselves are not AEs, they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

AEs fall into the categories "non-serious" and "serious."

10.2 Reporting of Adverse Events

AEs will be recorded starting with the signing of the informed consent. All AEs will be collected through the follow-up visit of Treatment Period 2. AEs that have not been directly reported to the Investigator will be promptly conveyed to the Investigator by the study staff. Investigators will additionally review any AE source documents and the subject's medical records, on a regular basis during the course of the study.

Beginning at the screening visit, and continuing for the duration of the study, subjects must be instructed to record any new AEs on the study specific symptom log. Subjects should bring the log to every clinic visit; where it will be retrieved for review by study staff prior to re-dispensing it (or issuing a new log) to the subject.

Any AE still unresolved at the Treatment Period 2 Follow-up Visit 10 (Day 36) or at the Premature Discontinuation Visit will be followed by the Investigator for at least 30 days from the last dose of investigational product. All unresolved AEs that were reported by the Investigator to be

probably drug related should be followed until the events are resolved/stabilized, the subject is lost to follow-up, or the AE is deemed irreversible.

Serious AEs must be submitted to the Sponsor within 24 hours of their discovery, even if the full information about the event is not yet available. These events should also be reported to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) as needed based on local requirements.

10.2.1 Severity of Adverse Events

All adverse events will be reported and graded, if possible, by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or later:
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

The severity of adverse events that cannot be graded by the most current version of CTCAE will be categorized as follows:

- Grade 1 – Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 – Mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 – Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible
- Grade 4 – Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required hospitalization or hospice care probable
- Grade 5 – Death

10.2.2 Relationship to Investigational Product

Association or relatedness to the investigational product will be graded as either "definitely related", "probably related", "possibly related", "unlikely related", or "not related". Determination of relatedness includes:

DEFINITELY RELATED – The adverse event:

- Follows a reasonable temporal sequence from administration of the study intervention
- Follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping
- Reappearance of the event on repeated exposure that could not be reasonably explained by the known characteristics of the subject's clinical state

PROBABLY RELATED – The adverse event:

- Follows a reasonable temporal sequence from investigational product administration

- Abates upon discontinuation of the investigational product
- Cannot be reasonably explained by the known characteristics of the subject's clinical state.

POSSIBLY RELATED – The adverse event:

- Follows a reasonable temporal sequence from investigational product administration
- Could have been produced by the subject's clinical state or by other modes of therapy administered to the subject

UNLIKELY RELATED – The adverse event:

- Does not follow a reasonable temporal sequence from investigational product administration
- Is readily explained by the subject's clinical state or by other modes of therapy administered to the subject

NOT RELATED – The adverse event:

- Clearly not related to the investigational product and another cause of the event is most plausible
- A clinically plausible temporal sequence is inconsistent with the onset of the event
- Study intervention and/or causal relationship is considered biologically implausible

10.2.3 Adverse Event of Special Interest

As part of a formal investigation of a drug that is classified as CNS active drug within the opioid drug class, certain adverse events will be documented in more detail as part of the analysis to determine any abuse potential of nalbuphine. If a subject spontaneously reports an event, a symptom or a subjective experience that fits any of the 4 categories of AEs described below, that event should be probed with open-ended questions, such as "Can you tell me more about that?" or "Have you ever experienced that kind of feeling before?". The goal is to better understand the context and the potential clinical significance of the event or subjective experience. Importantly, this probing and additional dialogue should take place **ONLY if the subject spontaneously reports such an event or experience**. Pro-active or suggestive questioning is not recommended, since the objective is to understand what the subjects themselves identify as new and different.

Specifically, terms that relate to the following types of events should trigger the collection of additional information under the AESI section of the Adverse Event eCRF:

Categories of Special Interest:

- Experiences or events suggestive of euphoria, such as elation, exhilaration, feeling a sense of exaggerated well-being, or feeling intoxicated.
- Experiences or events suggestive of mood changes or effects, such as reports of sedation, stimulation, or impaired attention/cognition. For example, descriptions of: somnolence,

sedation, lethargy; or agitation, anxiety, restlessness; or abnormal behaviors, labile affect, and depressed mood; or poor attention, and mental or memory impairment.

- Events or descriptions that suggest dissociative or psychotic experiences, such as reports of disorientation, abnormal thoughts, hallucinations, illusions or delusions.
- Observations that suggest events of drug abuse, misuse, dependence or withdrawal. These experiences or observations may be reported by the subject spontaneously (such as reports of feeling addicted, craving investigational product, or complaints of withdrawal after stopping the investigational product). The AE may also be based on direct observations made by the Clinician and/or study staff that suggest inappropriate use of the drug, drug tampering or drug diversion. For example, repetitive or significant single-time events of missing tablets in drug accountability assessments.

The AESI section of the AE eCRF provides for recording the following details about any events meeting the characteristics described above:

- A description of the AE event in the subject's own words.
- The estimated time between the subject's most recent dose prior to the AE, and the onset time of that AE (e.g., X minutes or Y hours between preceding dose and AE onset).
- Any prior history of the same, similar or related symptoms or events, and any relevant prior diagnoses, treatments or additional details from the subject (if a subject reports dizziness, do they have a history of dizziness, vertigo or any past diagnosis of Meniere's disease?).
- Investigator comments and/or assessment.

Finally, the development of a confirmed pattern of behavior that results in a new diagnosis of drug dependency or drug abuse should be reported as an SAE.

10.3 Abnormal Laboratory Values/Vital Signs/Electrocardiograms/Physical Examinations

Laboratory abnormalities will be recorded as adverse events only if they are associated clinical symptoms/events and they worsen following the start of investigational product treatment. Clinically significant findings noted prior to the start of investigational product treatment will be recorded as medical history. The recorded adverse event will indicate the underlying abnormality or diagnosis as opposed to the observed deviation in laboratory results if the diagnosis is known.

Clinically significant worsening in physical examination, vital sign, and ECG findings following start of investigational product treatment will be recorded as adverse events. Clinically significant findings noted prior to the start of investigational product treatment will be recorded as medical history.

10.4 Deaths

Should a death occur within the study period, or within 60 days after the last administration of investigational product, an adverse event form and an SAE form should be completed, detailing the adverse event that resulted in death (Note: death is an outcome, not an event). The SAE must

be reported to the Medical Monitor within 24 hours of the Investigator becoming aware of the event. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

10.5 Overdose

The effects of nalbuphine may be reversed with opioid antagonists such as naloxone. Please see the Guidance to the Investigator section of the Investigator's Brochure for additional information.

10.6 Pregnancy

Female subjects who become pregnant should be immediately discontinued from the study if they have not yet received investigational product. If a subject is found to be pregnant after she has received investigational product, she should discontinue dosing, complete all end-of-study procedures, and be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. While pregnancy itself is not considered an adverse event or SAE, any pregnancy complications or less than a healthy, normal outcome will be recorded as an adverse event or SAE.

10.7 Serious Adverse Events

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability and/or incapacity
- Results in a congenital anomaly or birth defect

A hospitalization is defined as an inpatient admission lasting 24 hours or more. Visits to urgent care centers and emergency departments that do not result in admission to a hospital for 24 hours will not be considered hospitalizations. Hospitalizations for elective procedures, defined as any procedure that was planned prior to signing of the informed consent will not, in and of themselves, be considered to fulfill criteria for an SAE.

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

Medical and scientific judgment should be exercised in deciding whether expedited 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered to be SAEs.

10.8 Reporting Serious Adverse Events

Investigators and other site personnel must inform appropriate PAREXEL International Corp. (PAREXEL) representatives of any SAE that occurs (whether or not attributable to the investigational product) in the course of the study within 24 hours of when he or she becomes aware of it.

All SAE reports must be submitted to the following within 24 hours:

PAREXEL International

E-mail: [redacted]

Fax No.: [redacted]

Tel No.: [redacted]

The PAREXEL representative will work with the Investigator to compile all the necessary information and ensure that the appropriate Sponsor representative receives a report within 1 day (24 hours) for any and all SAEs. Follow-up information on SAEs must also be reported by the Investigator within the same time frames.

11 STATISTICAL EVALUATION

As a companion to this protocol and in an effort to provide a more detailed explanation of the statistical methodology to be used for this study, a statistical analysis plan (SAP) will be developed prior to locking the database and before unblinding the randomization.

11.1 Sample Size and Power

The planned sample size of 44 subjects for the final analysis (22 per sequence) provides at least 80% power to detect a 40% reduction in Day 22 daytime cough frequency (coughs per hour) with NAL ER tablet treatment compared to placebo tablets at the 5% significance level (2-sided). This assumes a CV of 1.00 in log-transformed Day 22 cough frequencies. The CV estimated from *Kelsall et al (2011)* data on chronic cough in patients without esophageal catheterization is 1.12; because Kelsall et al data was on 24-hour cough (including nighttime cough, a period of lower coughing rate) and were not taken in a sample of IPF patients only, it is believed that the CV will be lower than in Kelsall et al data. If the CV is larger than planned at 1.25, this sample size provides > 80% power to detect a 50% reduction from placebo to NAL ER. Alternatively, if the CV is 0.75, this sample size provides > 80% power to detect a 34% reduction from placebo to NAL ER.

A total of approximately 60 subjects will be randomized to ensure complete data from at least 44 subjects, assuming up to potentially a 26% dropout rate.

A statistical update on this Proof-of-Concept (POC) study may be conducted when a minimum of 12 subjects have completed both study periods for the purposes of determining whether POC can be established prior to complete enrollment of the study.

The analysis will be based on conditional power (CP). Futility will be declared if the CP is < 10%, while efficacy will be declared if the CP > 80% (*Mehta and Pocock, 2010*). If the CP is at least 41%, the number of subjects per treatment arm may be changed to recover the targeted power of 80%. If it is evident that the outcome is influenced by a baseline imbalance in disease characteristics then the baseline imbalance will be taken into account in supplemental analyses.

11.2 Statistical Analysis Sets

11.2.1 Safety Population

The safety population will consist of all randomized subjects who have received at least a single dose of investigational product. The safety population will be used in all safety analyses.

11.2.2 Completers Population

The completers population will consist of all subjects who received both study treatments and completed both treatment periods in the study. The completers population will be used in the efficacy analyses.

11.3 Statistical Methods

11.3.1 General Principles

Summary statistics will be presented by treatment group. For continuous variables, unless otherwise stated, the number of available observations (n), mean, standard deviation, median, and range will be provided. For categorical variables, the number and percentage in each category will be displayed.

11.3.2 Missing Data

Missing or dropout data will not be imputed for the purpose of data analysis except for binary "responder" type of efficacy endpoints.

11.4 Demographic and Baseline Characteristics

Demographics and baseline disease characteristics, medical history, laboratory data, and physical examination findings will be summarized descriptively by treatment group.

11.5 Subject Disposition

Subject disposition will be summarized, including the reasons for discontinuation. The number of subjects in each analysis population will be displayed and an accounting of exclusions from each study population will be provided.

11.6 Concomitant Medications

Concomitant medications will be tabulated by Anatomical and Therapeutic Class (ATC) of World Health Organization (WHO) drug, preferred term, and treatment group. A medication's usage will be considered concomitant if it was started or continued after administration of the study medication.

11.7 Analysis of Efficacy Data

The primary efficacy endpoint of percent change in daytime cough frequency (coughs per hour) will be analyzed using a mixed-effects model with sequence, treatment, and time (Day 22) as fixed effects, the baseline value as a covariate, site as a random effect, and subject as a random repeated effect. There will be no imputation for dropouts or missing data for assessments not completed at study visits. A log transformation will be applied to daytime cough frequency; in the presentation of results, log-scale fitted mean treatment group differences at Day 22 will be back-transformed to fitted ratios of geometric means.

As a sensitivity analysis, a negative binomial model will be fitted with the number of coughs at Day 22 as the outcome, with terms for sequence, treatment, and time, as well as baseline cough frequency and subject, and duration of daytime (in hours) as an offset. An autoregressive covariance structure will be assumed for study visits, and the site random effect will use an unstructured covariance matrix.

Secondary efficacy endpoints will be summarized using descriptive statistics. For continuous endpoints (e.g., change from baseline), summaries will include mean, median, standard deviation, minimum, and maximum. For discrete variables (e.g., frequency), summaries will include number of instances and percentage of total instances for that category or time period.

11.8 Analysis of Safety Data

11.8.1 Adverse Events

The incidence of adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) body system classification and preferred term. All TEAEs will be summarized overall and for each body system and preferred term by treatment group, relationship to investigational product, and severity. For tabulations by severity, only a subject's most severe event within the category (e.g., overall, body system, or preferred term) will be counted. Adverse events will be dichotomized into "related" (probably and possibly) and "unrelated" (unlikely). "Treatment-emergent" will be defined as starting or worsening after the first dose of investigational product. If the start date is missing, the event is assumed to be treatment-emergent. All SAEs will be tabulated.

AESIs that code to the most relevant abuse-related MedDRA preferred terms will be tabulated and descriptive narratives will be written. Additional adverse events that are considered "possibly related to abuse potential" will be tabulated separately.

11.8.2 Vital Signs

Vital signs, including blood pressure, heart rate, and respiration rate, body temperature, pulse oximetry, and weight will be summarized by treatment group at baseline and at each scheduled visit.

11.8.3 Clinical Laboratory Assessments

Clinical safety laboratory data will be summarized descriptively by treatment group at baseline and subsequent scheduled visits. Summaries of safety laboratory parameters will include the first measurement of each scheduled assessment but repeat assessments done at the same study time point will not be included in summary calculations. Laboratory data will also be listed by treatment, subject, and visit. Listings will include scheduled, unscheduled, and repeat evaluations. A listing of markedly abnormal values, as defined in the SAP, will additionally be generated.

11.8.4 Physical Examinations

Abnormal physical examination findings that suggest a clinically significant worsening from baseline will be reported as adverse events and analyzed as such. Clinically significant findings noted prior to start of investigational product treatment will be recorded as medical history and analyzed as such.

11.8.5 Electrocardiograms

Electrocardiograms are to be reviewed locally for safety and read centrally by a core ECG laboratory with real-time feedback to clinical sites regarding any findings relevant to subject inclusion or withdrawal. Once the database is complete, ECG data (e.g., heart rate, PR, QTcF intervals) will be presented in listings by subject and summarized by collection date and time. A complete ECG assessment will be documented in a separate report from the central ECG laboratory.

11.8.6 Spirometry

Spirometry parameters, including the FVC, will be summarized by treatment group at baseline and the Day 21 visits of each treatment period.

11.9 Pharmacokinetics Analysis

Nalbuphine (parent and metabolites) plasma concentration data will be listed by collection time and nalbuphine dose where applicable. Further PK analyses may be conducted if data allow.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Conduct of the Study

The Sponsor shall implement and maintain quality control and quality assurance procedures with written Standard Operating Procedures (SOP) to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study is to be conducted according to globally accepted standards of GCP (as defined in the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), November 2016), in agreement with the latest revision of the Declaration of Helsinki, and in keeping with local regulations.

The Investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Investigator should maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/IEC, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the subject having to be withdrawn from the study and render that subject non-evaluable.

12.2 Study Monitoring

Monitoring and auditing procedures, developed or endorsed by the Sponsor, will be followed to comply with GCP guidelines. Access to the on-site study documentation and medical records will be ensured.

The study will be monitored by the Sponsor or its designee. Throughout the course of the study, the clinical research associates (CRA) will make frequent contact with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the eCRF will be reviewed for completeness and adherence to the protocol. As part of the data monitoring, source documents must be made available to the CRA for review. The CRA will also perform investigational product drug accountability and subject compliance checks and will request to perform a review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct and safety oversight.

Upon completion of the study, the CRA will arrange for a final review of the study files, after which the files should be secured for the appropriate time period. The Investigator, or appointed delegate, will meet with the CRA during the on-site visits and will cooperate in providing the documents for inspection and responding to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of the Sponsor or regulatory agencies.

During the course of the study, certain sites may be chosen and scheduled for a routine audit by the Sponsor or its designee as part of the Sponsor's normal processes.

13 ETHICS

13.1 Independent Ethics Committee/Institutional Review Board

Prior to initiation of the study, the Investigator will submit the study protocol, sample informed consent form (ICF), and any other documents that pertain to subject information, recruitment methods such as subject diaries, and advertisements, to the IRB/IEC. The Investigator must also submit any other information that may be requested to the IRB/IEC for review and approval. The Investigator will request that the IRB/IEC provide written approval of the study and will keep on file records of approval of all documents pertaining to this study. A letter confirming the approval must be provided to the Sponsor/CRO prior to initiation of this study.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site, as well as other adverse event reports received by the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IRB/IEC approval or renewal throughout the duration of the study.

13.2 Written Informed Consent

Potential subjects must provide written consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An ICF that includes information about the study will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the potential subject. Where required by local law, the person who informs the potential subject must be a physician.

After reading the ICF, the potential subject must give consent in writing. The subject’s consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

A copy of the signed ICF must be given to the subject. The original signed ICFs will be retained by the Investigator.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

14 DATA HANDLING AND RECORD KEEPING

14.1 Case Report Forms/Source Data Handling

The Investigator, or designee, will enter study data required by the protocol into an electronic data capture (EDC) system. The CRA will visit each study site, at a frequency documented in the monitoring plan, to review the eCRF for completeness and accuracy. Any discrepancies found between source documents and the completed eCRF will be entered as a discrepancy in the EDC system by the CRA. Appropriate study site personnel should then address those discrepancies in the EDC system. Uniform procedures for eCRF correction (queries) will be discussed during the study site initiation visits and will be documented in the study operations manual.

Data from eCRF and other external data sources will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Computerized and manual procedures should be used to review and check data from eCRF and data from other external sources for omissions, apparent errors, and values that may require further clarification. Data queries requiring clarification should be documented, and the study site should be requested to review and resolve the queries. Only authorized personnel can make corrections to the clinical database, and all corrections should be documented in an audit trail.

Adverse events will be coded using the most current MedDRA version. Prior and concomitant medications will be coded according to the WHO Drug Dictionary.

14.2 Retention of Essential Documents

14.2.1 Access to Records

The study may be subject to audit by the Sponsor, its designee, or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. The Investigator should notify the Sponsor promptly of regulatory authority audits that are scheduled and must forward copies of any findings or audit reports to the Sponsor promptly. Examples of such documents are outlined below but are not an exhaustive list:

- Signed ICFs for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/IEC
- Composition of the IRB/IEC or other applicable statement
- Record of all communications between the Investigator and Sponsor (or CRO)
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study and their signatures
- Copies of eCRFs and of documentation of corrections for all subjects

- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring and review of all appropriate study documentation, as well as on-site review of the procedures employed in data collection, where clinically appropriate.

14.2.2 Retention of Records

When the study is completed, the Investigator must retain the essential documents for as long as needed to comply with regulatory guidelines and Sponsor requirements. The Investigator will notify the Sponsor prior to moving or destroying any of the study documents. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. The Investigator should take measures to prevent any accidental or premature destruction of these documents.

15 PUBLICATION POLICY

The Sponsor will retain the ownership of all data. When the study is complete, the Sponsor will arrange the analysis and tabulation of data. A clinical study report will then be prepared, which may be used for publication, presentation at scientific meetings, or submission to regulatory authorities. All proposed publications based on this study will be subject to the Sponsor's approval requirements.

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APPENDICES

[redacted]

Summary of Changes:

APPENDIX 11: Summary of Changes

Appendix 11 Summary of Changes

Amendment 6 Rationale:

Clinical Research Protocol TR12 v7.0 (14 December 2021) was produced for the following purposes:

- To allow for a potential statistical update when a minimum of 12 subjects have completed both study periods for the purposes of determining whether POC can be established prior to complete enrollment of the study.
- To update the sponsor contact information.
- To make other administrative updates as needed for consistency with the above changes (additions to abbreviations list, updated document date and version number).

Changes*	Location of changes	Rationale
Sponsor contact: [redacted]	Page 1	Change in staff.
The planned sample size of 44 subjects for the final analysis (22 per sequence) provides at least 80% power to detect a 40% reduction in Day 22 daytime cough frequency (coughs per hour) with NAL ER tablet treatment compared to placebo tablets at the 5% significance level (2-sided). … Alternatively, if the CV is 0.75, this sample size provides > 80% power to detect a 34% reduction from placebo to NAL ER. A total of approximately 60 subjects will be randomized to ensure complete data from at least 44 subjects, assuming up to potentially a 26% dropout rate. A statistical update on this Proof-of-Concept (POC) study may be conducted when a minimum of 12 subjects have completed both study periods for the purposes of determining whether POC can be established prior to complete enrollment of the study. The analysis will be based on conditional power (CP). Futility will be declared if the CP is < 10%, while efficacy will be declared if the CP > 80% (*Mehta and Pocock, 2011*). If the CP is at least 41%, the number of subjects per treatment arm may be changed to maintain the targeted power of 80%. If it is evident that the outcome is influenced by a baseline imbalance in disease characteristics then the baseline imbalance will be taken into account in supplemental analyses.	11.1 Sample Size and Power	To allow for a assessment for the purposes of determining whether POC can be established prior to complete enrollment of the study.

*Additions shown as underlines and deletions shown with strike through.

Amendment 5 Rationale:

Clinical Research Protocol TR12 v6.0 (11 June 2021) was produced for the following purposes:

- To provide clarification on the QTcF values to prevent exclusion of subjects who present with Right Bundle Branch block
- To clarify exclusion criteria.
- To clarify study procedures.
- To correct minor administrative errors.

Change	Location of Text that Changes	Rationale
Clarification of exclusion criterion #30 **Previous Wording**: QTcF interval > 450 ms on any screening ECG tracing (triplicate). **Revised Wording:** QTcF interval >450 ms (mean of 3 screening ECG QTcF values) if QRS <120 ms (mean of 3 screening ECG QRS values); QTcF interval >480 ms in the presence of Right Bundle Branch Block (RBBB) and/or QRS ≥ 120 ms	Synopsis: Exclusion Criteria Section 7.3 Exclusion Criteria	To more accurately capture the electrophysiological criteria that can be identified by ECG that will be the basis for excluding subjects who would be at potential risk for developing a clinically significant cardiac arrhythmia. In the presence of RBBB measured on ECG, the QRS is at least 30 ms wider than would otherwise be recorded in subjects with normal QRS duration. The QT interval will therefore be at least 30 ms longer in duration. In the absence of RBBB, prolonged QRS complexes are commonly noted in pulmonary disease patients, so the increase in QT due to a wide QRS may be observed in patients who do not have typical RBBB, but instead have a nonspecific intraventricular conduction defect (IVCD).

Change	Location of Text that Changes	Rationale
Clarification of Exclusion Criterion (#32) **Previous Wording:** Use of a medication having a "known risk" of Torsade de Pointes (categorized as "KR" on the Credible Meds® website) is not permitted at entry or during the study (See *Appendix 9*). Medications associated with a potential risk of QT prolongation, but not clearly associated with Torsade de Pointes, are permitted at study entry if the following criteria are met: • Subject has been given medication at stable doses for a full 4 weeks prior to screening. • Medication dose will not be increased after screening, or during the study, and it is anticipated that the subject will receive the medication for the entirety of the study • QTcF on any ECG tracing obtained at Screening is ≤ 450 ms **Deleted Wording:** **QTcF on any ECG tracing obtained at Screening is ≤ 450 ms**	Synopsis: Exclusion Criteria Section 7.3 Exclusion Criteria	The appropriate QTcF exclusion has been added to exclusion criterion #30 and no longer accurate or required under exclusion #32

Change	Location of Text that Changes	Rationale
Clarification to the withdrawal Criteria relating to QTcF **Previous Wording**: The subject develops a QTcF > 500 ms or presents with a confirmed increase from baseline of > 60 ms. **Revised Wording:** Develops a QTcF > 500 ms (mean of 3 ECG QTcF values) in subjects who were randomized without ECG findings of RBBB and/or QRS ≥ 120 ms. Develops QTcF > 530 ms (mean of 3 ECG QTcF values) in subjects who were randomized with ECG findings of RBBB and/or QRS ≥ 120 ms. Increase from QTcF baseline of > 60 ms (mean determination from 3 ECG values) .	Section 7.4: Withdrawal Criteria	To accurately reflect an electrophysiologically meaningful change on ECG parameters that would indicate a potential cardiac arrhythmia risk to a subject if they continued in the study.

Change	Location of Text that Changes	Rationale
Previous Wording: Electrocardiograms will be reviewed locally for safety by the Investigator and/or their designee and read centrally for clinical significance and ECG intervals (PR, RR, QRS, QT, and QTcF using nomogram table), rate, rhythm, and other clinically significant abnormalities (e.g., left ventricular hypertrophy, pathological Q-waves). If a subject develops a QTcF > 500 ms or presents with an increase from baseline > 60 ms, the ECG will be repeated at least 30 minutes later. If these parameters are confirmed on the second ECG by the Core ECG laboratory, the subject will be discontinued from the study. **Revised Wording:** Electrocardiograms will be reviewed locally for safety by the Investigator and/or their designee. **The ECGs will be** read centrally for **the purpose of meeting the ECG study inclusion criteria, study withdrawal criteria** and ECG intervals (PR, RR, QRS, QT, and QTcF using nomogram table), rate, rhythm, and other clinically significant abnormalities (e.g., left ventricular hypertrophy, pathological Q-waves)	Section 8.4.6 Electrocardiogram Assessments	To clarify Local ECG read is for safety purposes and central ECG read is related to subject inclusion/withdrawal.

Change	Location of Text that Changes	Rationale
Deleted wording: **If a subject develops a QTcF > 500 ms or presents with an increase from baseline > 60 ms, the ECG will be repeated at least 30 minutes later. If these parameters are confirmed on the second ECG by the Core ECG laboratory, the subject will be discontinued from the study**	Section 8.4.6 Electrocardiogram Assessments	QTcF clarifications and appropriate actions to be taken clarified in section 7.4 for subject discontinuation.
Previous wording: Electrocardiograms are to be reviewed locally and read centrally by a core ECG laboratory with real-time feedback to clinical sites regarding any findings relevant to safety. **Additional wording**: Electrocardiograms are to be reviewed locally **for safety** and read centrally by a core ECG laboratory with real-time feedback to clinical sites regarding any findings relevant to **subject inclusion or withdrawal**. **Deleted wording**: Electrocardiograms are to be reviewed locally and read centrally by a core ECG laboratory with real-time feedback to clinical sites regarding any findings relevant to **safety.**	Section 11.8.5 Electrocardiograms	To clarify Local ECG read is for safety purposes and central ECG read is related to subject inclusion/withdrawal.
Administrative changes throughout the protocol	Various sections of the revised protocol document	To provide functional and administrative clarifications.