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

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Trevi Therapeutics, Inc.

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Statistical Analysis Plan

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SPONSOR SIGNATURE PAGE

This document has been approved by sponsor and signed in the separate signoff form by the following.

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Trevi Therapeutics, Inc.

PAREXEL SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 0.1	20Dec2019	New document
Draft 0.2	04Feb2020	Comments resolution
Draft 0.3	01Feb2021	Updates per new Protocol Amendments
Draft 0.4	03May2021	Minor comments implementation
Final 1.0	08Feb2022	Updates per new Protocol Amendment and CRF Version. Finalization
Draft 1.1	04May2022	Update the SAP to reflect current statistical practices in using full analysis set as the primary analysis set and provide corresponding clarifications to Analysis and TFLs Include information on Interim Analysis Include supplementary tables
Draft 1.2	31May2022	Comments resolution
Draft 1.3	07Jun2022	Adjustments due to new Vitalograph structure: the parameters for 24h cough frequency and asleep time cough frequency will be received by the vendor and not derived by PAREXEL.
Final 2.0	Date of last signature	Document Finalization

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
AE-IPF	Acute exacerbations of IPF
AESI	Adverse event of special interest
ATC	Anatomical-Therapeutic-Chemical
BDRM	Blinded Data Review Meeting
BID	Twice daily
BLQ	Below limit of quantification
CGI-C	Clinical Global Impression of Change
CfB	Change from Baseline
CIs	Confidence Intervals
CTCAE	Common Terminology Criteria for Adverse Events
DLco	Diffusing capacity of the Lung for carbon monoxide
Cough monitor	Wearable digital cough monitor hookup (24-hour recording) provided by external vendor Vitalograph®
CV%	Coefficient of variation
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ER	Extended release
E-RS	Evaluating Respiratory Symptoms
EXACT	EXAcerbation of Chronic pulmonary disease Tool
FAS	Full Analysis Set
GM	Geometric mean
GMR	Geometric mean ratio
IA	Interim Analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IPF	Idiopathic pulmonary fibrosis
LLOQ	Lower limit of quantification

Abbreviation / Acronym	Definition / Expansion
MedDRA	Medical Dictionary for Regulatory Activities
NAL ER	Nalbuphine extended-release
NC	Not calculable
NIH	National Institutes of Health
NS	No sample
OTC	Over-the-counter
PD	Protocol deviation
PRO	Patient-Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System Organ Class
SOWS	Subjective Opiate Withdrawal Scale
TEAE	Treatment Emergent Adverse Event
UIP	Usual interstitial pneumonia
US	United States
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is 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. 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).

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 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.

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. Opioid class drugs are known to reduce pain that is mediated via peripheral sensitization-induced neuronal signaling.

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol. This SAP covers the planned analysis of all data collected on paper (source documents /case report forms [CRFs]), captured electronically in Data Labs, and provided by external vendors.

This SAP will be finalized at least 1 month prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. SAP amendments necessitated by protocol amendments will be issued within 1 month of the published protocol amendment. Any deviations from the protocol will be addressed in Section 4.14: Changes in the Conduct of the Study or Planned Analysis. If circumstances should arise during the study rendering this analysis inappropriate or if improved methods of analysis should come to light, different analyses may be

made. If this occurs, the sponsor will determine how the revision impacts the study and how the SAP revision should be implemented. The details of the revision will be documented and described in the clinical study report (CSR).

The structure and content are based upon ICH requirements as detailed in ICH E3 Structure and Content of Clinical Study Reports [1] and ICH E9 Statistical Principles for Clinical Trials [2].

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 7.0 (December 14, 2021)
- electronic Case Report Form (eCRF), Version 5.0 (August 06, 2021)

Of note: this is an early phase Proof of Concept study which started in February 2019; at this development stage it is not deemed necessary to implement the estimand framework as introduced by ICH E9 Addendum: Statistical Principles for Clinical Trials.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

- 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.

2.2 Secondary Objective(s)

- 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 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 Clinical Global Impression of Change (CGI-C) over time by treatment measured at Day 21.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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.

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.

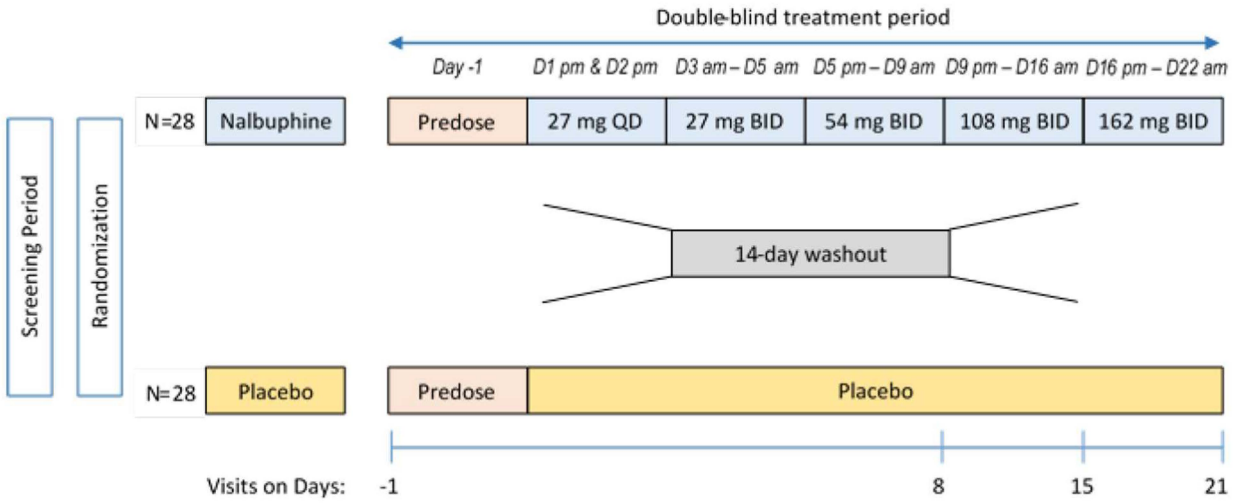
Study visits will include screening to determine eligibility, and for each treatment period: visits at Day -1 for baseline assessments, at Days 8, 15, and 21 during treatment, and a follow-up at the end of the 2-week washout period. At study screening and the Day 21 visits during each treatment period, subjects will have blood drawn for safety analysis. Nalbuphine (and/or metabolites) plasma concentration will also be measured 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.

The schedule of assessments is provided in Appendix 1 and Appendix 2.

Figure 1 – Study Schematic



3.2 Endpoints and Associated Variables

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.
- 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, 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.

3.2.1 Efficacy Variables

Cough frequency is recorder via a wearable digital cough monitor hookup (24-hour recording) provided by external vendor Vitalograph® hereby referred to as 'cough monitor'.

Baseline (pre-treatment) recording of cough frequency will be obtained at Visit 2 (day -1) for Treatment Period 1 and at Visit 6 (day -1) for Treatment Period 2. Period 1 baseline will be taken as the general study baseline as explained in the baseline definition at section 4.2.3 of this SAP.

Cough frequency will also be recorded at Visit 5 (day 21) for Treatment Period 1 and at Visit 9 (day 21) for Treatment Period 2.

Cough frequency will be captured in a 24-hour recording.

External vendor Vitalograph® will derive and provide daytime cough frequency at each pertinent visit.

3.2.1.1 Primary Efficacy Variable

Daytime cough frequency at Day 22 is the primary efficacy variable.

Hourly daytime cough frequency is derived by the external vendor and will be received as a transfer SAS dataset named 'FA' under variable FAORRES when FATEST='Cough average Score at daytime'.

"Daytime" is defined as the time the subject is awake in the 24 hours after the digital cough monitor is applied for use. Events, including sleep, late attachment and device removal, are identifiable in recording via combined assessment of cough monitor algorithms and specially trained cough analysts which will identify these periods from the waveform generated and by the content of the sounds heard. Vitalograph® analysts are trained in differentiating sleep periods from the subject being asleep. Consequently, identification of the possible sleep time is done by Vitalograph® analysts and will be indicated in the data transfer as date and time of sleep start and end.

Of note:

- If the patient gets up for a short period in the night i.e. use the bathroom or drink a glass of water, this will be counted as sleep time.
- If the patient gets up for a longer period, this will be classed as awake time.
- If two or more periods of sleep exist in a recording the start and end times of each sleep period will be identified.

The following events will be recorded and collected in the data transfer, together with start and end date as appropriate:

Table 1 – Cough Monitor Events

Event Name	Description
Sleep	Sleep Period
Device Not Attached	The recording is on, but the device is not attached to the subject
Recording Ended Early	Recording duration is shorter than what was expected
Flagged Area	An area/period of the recording where there is an issue with the result that this period cannot be analyzed.

The Vitalograph® data transfer will hold the daytime average coughs per hour based on the following calculation, rounded to two decimal places:

Daytime cough frequency = ((total cough events for a session not within Sleep, Device Not Attached, Recording Ended Early, Flagged Area event periods) / (recording length in seconds - Sleep, Device Not Attached, Flagged Area event period durations)) x 3600. A session is defined as that 24-hour period when cough recording is taking place for an individual subject. For a session with 'Recording Ended Early', the recording early end datetime will be the end datetime for the session. No events will be collected after the recording early end datetime.

Recording of daytime cough frequency is expected in treatment period 1 at Visit 2 (Study baseline: starting on day -1 and ending at day 1 prior to first IMP intake) and Visit 5 (starting on day 21 and ending on day 22), and in treatment period 2 at Visit 6 (Baseline: starting on day -1 and ending at day 1 prior to first IMP intake) and Visit 9 (starting on day 21 and ending on day 22).

A 24-hour recording is required per protocol at each appropriate visit. All recordings considered valid per Vitalograph® quality assessment will be used in analysis, irrespective of actual duration. Cough frequency will be computed based on the actual recording duration.

For the primary endpoint analysis, daytime cough frequency will be log transformed on the natural log scale; ratios will be then calculated per subject per period as log (Visit cough / Study baseline cough) which would represent, upon back transformation and subtraction from 100%, a percent reduction in daytime cough frequency versus study baseline.

3.2.1.2 Secondary Efficacy Variables

3.2.1.2.1 24-hour cough frequency

24-hour cough frequency is defined as the total number of cough events recorded in a 24-hour period, divided by 24, rounded to the nearest 2 decimal places.

24-hour cough frequency per hour will be directly provided by Vitalograph® in the data transfer; this will be available in FA dataset under variable FAORRES when FATEST = 'Full Average Hourly Cough'.

The Vitalograph® data transfer will hold the 24-hour cough frequency average per hour based on the following calculation, rounded to two decimal places:

24-hour cough frequency = (total cough events for a session) / (recording length in seconds - Recording Ended Early, Device Not Attached, Flagged Area event period durations)) x 3600. A session is defined as that 24 hour period minus quality event periods when cough recording is taking place for an individual subject. For a session with 'Recording Ended Early', the recording early end datetime will be the end datetime for the session. No events will be collected after the recording early end datetime.

Of note: will be blank in the vendor file if the session is rejected.

For 24-hour cough frequency endpoint, a natural log transformation will be applied as described for daytime cough frequency in section 3.2.1.1.

3.2.1.2.2 Nighttime cough frequency

Nighttime cough frequency will be intended as the average while the subject is flagged as being asleep.

Nighttime (i.e., asleep) cough frequency is derived as the number of coughs counted during sleeping time, divided by duration of sleep time, rounded to the nearest 2 decimal places.

Nighttime (i.e., asleep) cough frequency per hour will be directly provided by Vitalograph® in the data transfer; this will be available in FA dataset under variable FAORRES when FATEST = 'Sleep Average Hourly Cough'.

The Vitalograph® data transfer will hold the asleep cough frequency average per hour based on the following calculation, rounded to two decimal places:

Nighttime cough frequency = ((total cough events for a session within Sleep event period) / (recording length in seconds within Sleep event period)) x 3600.

Of note: will be blank in the vendor file if the session is rejected.

For nighttime cough frequency endpoint, a natural log transformation will be applied as described for daytime cough frequency in section 3.2.1.1.

3.2.1.2.3 EXACT 14-item e-Diary Tool

A copy of the daily diary tool EXACT version 1.1 is provided in Protocol Appendix 1.

The EXACT is a 14-item Patient Reported Outcome (PRO) daily diary tool that was originally developed to quantify and measure exacerbations of COPD. Subjects will complete the EXACT scale via the study specific e-diary. E-diary tool will be completed each evening by the subject prior to bedtime, throughout study baseline to Period 2 Day 22 or premature discontinuation.

A higher score indicates a more severe condition.

Questionnaire is recorded daily, the record collected on the Day 22 visit date will be used as the post baseline value in the summary tables; if a record is not available on the exact date then the last assessment prior to the Day 22 visit date, within a window of 5 days prior to the visit date, will be used. Study baseline value will be the last assessment available prior to the first IMP intake (as defined in this SAP at section 4.2.3).

3.2.1.2.4 E-RS diary

The E-RS daily diary is a derivative instrument of the EXACT consisting of the 11 respiratory symptoms items contained within the 14-item EXACT that measures the effect of treatment on the severity of respiratory symptoms. 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 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, 0-17)
- cough (E-RS item 2; score range 0-4)
- sputum (E-RS items 3 and 4; score range, 0-8)
- 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.

Questionnaire is recorded daily, the E-RS breathlessness and cough items record collected on the Day 22 visit date will be used as the post baseline value in the summary tables; if a record is not available on the exact date then the last assessment prior to the Day 22 visit date, within a window of 5 days prior to the visit date, will be used. Study baseline value will be the last assessment available prior to the first IMP intake (as defined in this SAP at section 4.2.3).

3.2.1.2.5 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”).

A copy of the Cough Severity Numerical Rating Scale is provided in Protocol 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 in treatment period 1 at Visit 2 (Study baseline), Visit 3 (day 8), Visit 4 (day 15) and Visit 5 (day 21), in treatment period 2 at Visit 6(Baseline), Visit 7 (day 8), Visit 8 (day 15) and Visit 9 (day 21) and at premature discontinuation visit.

Questionnaire is recorded daily, the record collected on the Day 22 visit date will be used as the post baseline value in the summary tables; if a record is not available on the exact date then the last assessment prior to the Day 22 visit date, within a window of 5 days prior to the visit date, will be used. Study baseline value will be the last assessment available prior to the first IMP intake (as defined in this SAP at section 4.2.3).

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

The PROMIS is a US National Institutes of Health (NIH) funded initiative to develop and validate PROs for clinical research and practice.

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 Protocol Appendix 3. This scale will be administered via the study specific e-diary during onsite visits (in treatment period 1 at Visit 2 (Study baseline) and Visit 5 (day 21), in treatment period 2 at Visit 6 (Baseline) and Visit 9 (day 21) and at premature discontinuation visit.

Questionnaire is recorded daily, the record collected on the Day 22 visit date will be used as the post baseline value in the summary tables; if a record is not available on the exact date then the last assessment prior to the Day 22 visit date, within a window of 5 days prior to the visit date, will be used. Study baseline value will be the last assessment available prior to the first IMP intake (as defined in this SAP at section 4.2.3).

3.2.1.2.7 Clinical Global Impression of Change Scale

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. The CGI-C can track clinical progress across time.

The CGI-C is provided in Protocol Appendix 5.

The CGI-C is collected in treatment period 1 at Visit 5 (day 21) and in treatment period 2 at Visit 9 (day 21).

3.2.2 Pharmacokinetic Variables

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

3.2.3 Safety Variables

3.2.3.1 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 definitions and analysis are reported in section 4.11.1 of this SAP.

3.2.3.2 Clinical Laboratory Tests

Clinical laboratory tests will be performed by a qualified central laboratory.

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.

Clinical laboratory tests will be collected at Screening, in treatment period 1 at Visit 5 (day 21), in treatment period 2 at Visit 6 (Baseline) and Visit 9 (day 21) and at premature discontinuation visit.

3.2.3.3 Pregnancy Tests

Urine and serum pregnancy tests will be performed for females of childbearing potential.

Urine pregnancy test will be collected at Screening, in treatment period 1 at Visit 2 (Study baseline) and Visit 6 (Follow-up), in treatment period 2 at Visit 10 (Follow-up) and at premature discontinuation visit.

Serum pregnancy test will be collected at Screening, in treatment period 2 at Visit 6 (Baseline) and at premature discontinuation visit.

3.2.3.4 Vital signs

Vital signs (resting blood pressure, heart rate, and respiratory rate), body temperature and pulse oximetry will be measured.

Vital signs will be collected at Screening, in treatment period 1 at Visit 6 (Follow-up), in treatment period 2 at Visit 10 (Follow-up) and at premature discontinuation visit.

3.2.3.5 Physical Examination

A physical examination will be performed at the screening visit, in treatment period 1 at Visit 6 (Follow-up), in treatment period 2 at Visit 10 (Follow-up) and at premature discontinuation visit.

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.

3.2.3.6 Electrocardiogram Assessments

ECGs will be performed in triplicate at Screening, in treatment period 1 at Visit 6 (Follow-up), in treatment period 2 at Visit 10 (Follow-up) and at premature discontinuation visit.

A standard ECG will be obtained according to the Schedule of Events and recorded prior to blood sampling. Electrocardiograms will be 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).

ECG can be repeated if a subject develops a QTcF > 500 ms, or presents with an increase from study baseline > 60 ms, this can be a cause for discontinuation from the study.

The mean of the triplicate ECGs parameters will be derived. If no repeats of ECG are performed, then the single assessment received will be used in analysis; if ECG was only repeated twice, mean of the two assessments will be used; in case of ECG quadruplicate or more, only the first three

assessments will be used for mean derivation. Unscheduled (including repeated) ECGs will not be included in the mean derivation.

3.2.3.7 Spirometry

Spirometry will be executed at Screening, in treatment period 1 at Visit 5 (day 21), in treatment period 2 at Visit 9 (day 21) and at premature discontinuation visit.

3.2.3.8 Diffusing capacity of the Lung for carbon monoxide (DLco)

DLco will be collected at Screening only.

3.2.3.9 Swallow Test

The Swallow Test will be assessed at Screening only.

3.2.3.10 Subjective Opiate Withdrawal Scale (SOWS)

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 Protocol Appendix 4. Subjects will complete the SOWS via the study specific e-diary.

3.2.4 Exploratory Variables

As an additional exploratory analysis, a flag will be derived for 30%, 50% and 75% reduction from baseline in daytime cough counts.

Daytime cough frequency change from baseline (CfB) will be derived as follow:

Daytime cough frequency CfB = (Day 22 cough frequency – Study baseline cough frequency) / Study baseline cough frequency) * 100.

Daytime cough frequency CfB will then be categorized as follow:

- Daytime cough frequency CfB < 30%
- Daytime cough frequency CfB ≥ 30% and <50%
- Daytime cough frequency CfB ≥ 50% and <75%
- Daytime cough frequency CfB ≥ 75%

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

With protocol version 5.0 as of 17 July 2020, on site assessments were consistently reduced to mitigate risk for subjects to be exposed to COVID19 pandemic. Data will be summarized based on schedule of events planned in protocol version 5.0, while all the data collected will be listed.

4.2.1 Treatment Period, Treatment and Sequence

In this Study, two treatment periods are planned: Treatment Period 1 includes visits from Screening (day -45 to -2) to Visit 6 follow-up (day 36); Treatment Period 2 include visits from Visit 6 Baseline (day -1) to Visit 10 follow-up (day 36).

Two treatments are planned for administration to each subject: NAL ER tablets and Placebo tablets.

Two sequences (arms) are also planned; subjects in sequence 1 will receive active NAL ER tablets followed by crossover Placebo tablets in Treatment Period 2; subjects in sequence 2 will receive Placebo tablets followed by crossover NAL ER tablets in Treatment Period 2.

4.2.2 Relative Study Day

4.2.2.1 Relative Study Day in Treatment Period 1

In Treatment Period 1, Study Day 1 is defined as the date of first investigational medicinal product (IMP) intake occurring on Treatment Period 1.

In Treatment Period 1, other study days are defined relative to the Study Day 1 as follow:

- assessments taken before the Treatment Period 1 first IMP administration:

  Relative Study Day = assessment date - Treatment Period 1 first IMP intake date

- assessments on or after the repeat administration:

  Relative Study Day = assessment date - Treatment Period 1 first IMP intake date + 1.

As soon as the first IMP intake occurs on Treatment Period 2, then the rules outlined in section 4.2.2.2 will apply.

4.2.2.2 Relative Study Day in Treatment Period 2

In Treatment Period 2, Study Day 1 is defined as the date of first IMP intake occurring on Treatment Period 2.

In Treatment Period 2, other study days are defined relative to the Study Day 1 as follow:

- assessments taken on or after Treatment Period 1 Visit 6 (Follow-up) and before the Treatment Period 2 first IMP intake:

  Relative Study Day = assessment date - Treatment Period 2 first IMP intake date

- assessments on or after the repeat administration:

  Relative Study Day = assessment date - Treatment Period 2 first IMP intake date + 1.

4.2.2.3 Relative Study Day at Visit 6

In most instances, the baseline visit for Treatment Period 2 will occur on the same calendar day as the Follow-up Visit 6 for Treatment Period 1; in this case, relative Study Day at Visit 6 will be calculated for Treatment Periods 1.

In the instance that baseline visit for Treatment Period 2 will occur on a different calendar day as the Follow-up Visit 6 for Treatment Period 1, then rules outlined in section 4.2.2.1 will apply to Follow-up Visit 6 for Treatment Period 1, while rules outlined in section 4.2.2.2 will apply to baseline visit for Treatment Period 2.

4.2.3 Baseline Definition

Unless otherwise specified, in this Study, two Baselines will apply:

'Study Baseline' coincides with the 'Period 1 Baseline' and is defined as the last available assessment prior to the first Treatment Period 1 IMP intake.

'Period 2 Baseline' is defined as the last available assessment prior to the first Treatment Period 2 IMP intake.

Unless otherwise specified, when this SAP refers generically to baseline and change from baseline, it is to be intended as the study baseline defined in this section.

If not otherwise stated, the primary and key secondary endpoints, as well as secondary and exploratory endpoints, will utilize study baseline for statistical models, descriptive and graphical analysis.

4.2.4 Data Listings

All original and derived parameters will be listed.

Listings will include both scheduled and unscheduled measurements; such measurements will appear in chronological order together with the scheduled time points.

All listings will be sorted by sequence (i.e. Arm 1: NAL-ER + Placebo; Arm 2: Placebo + NAL-ER), subject number and time (visit); actual treatment received at timepoint will always be displayed, as appropriate. Study baselines will be flagged in listings.

Unless otherwise specified, relative study day will be provided for each date, please refer to Section 4.2.2 for derivation of relative study days. Study days relative to Treatment Period 1 will be printed as 'TP1:XX' (where XX stays for a particular study day); similarly, study days relative to Treatment Period 2 will be printed as 'TP2:XX' (where XX stays for a particular study day). In most instances, the Baseline visit for Treatment Period 2 will occur on the same calendar day as the Follow-up Visit 6 for Treatment Period 1; in this case, 'TP1:XX' will be printed.

Unless otherwise specified, listings will be presented based on all screened subjects; Screen Failure subjects will be included as well under 'Screen Failure:'.

4.2.5 Data Summaries

Subject disposition, Demographics, Medical History, Treatment Exposure and Treatment Compliance tables will be summarized by sequence (see definition in section 4.2.1).

In efficacy and safety tables (including concomitant medications), results will be summarized under the actual treatment received (NAL-ER or Placebo) independently whether the NAL-ER (and Placebo) was received in Treatment Period 1 or 2. In other words, summaries will be presented by treatment received.

In most instances, the baseline visit for Treatment Period 2 will occur on the same calendar day as the Follow-up Visit 6 for Treatment Period 1; in any case, Visit 6 results will be used as Follow-up for Treatment Period 1, while the baseline for the Treatment Period 2 will be the study baseline (taking into account baseline definition from section 4.2.3).

Continuous data will be summarized in terms of the number of subjects with non-missing values, mean, standard deviation (SD), median, minimum and maximum, unless otherwise stated.

The following rules will apply to all descriptive statistic displays, where 'd' denotes the decimal places in the original reported value:

- n (number of non-missing observations): 0 decimal places (d.p.)
- Mean: d + 1 d.p.
- SD: d + 2 d.p.
- Median: d + 1 d.p.
- Minimum: d
- Maximum: d
- Statistics in percentage: 1 d.p.
- Confidence Intervals (CIs): d + 1 d.p.
- A maximum of 3 decimal places will be displayed.

All CIs will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator.

In general, for categorical variables showing multiple possible categories, these will be displayed following the within variable logic criteria; where such a logic criterium does not exist (example: gender, race, AE SOC, AE PT), categories will be displayed by overall descending frequencies.

4.2.6 Figures

In figures, results will be summarized based on the treatment (NAL-ER and Placebo) independently whether the NAL-ER (and Placebo) was received in Treatment Period 1 or 2.

Figures will be produced in black and white.

4.3 Software

All report outputs will be produced using a server-based SAS® version 9.3 or a later version in a secure and validated environment. The REPORT procedure (SAS PROC Report) will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures.

All report outputs will be provided to the Sponsor in RTF format.

4.4 Study Subjects

4.4.1 Disposition of Subjects

The patient disposition including the date the informed consent was signed, date of randomization, date of last dose and the primary reason for End of Study will be listed.

A by subject listing of violated Inclusion/Exclusion criteria will be presented.

A by subject listing of study visits will be presented.

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

Following disposition summaries will be based on all screened subjects:

- Number of subjects screened for entry into the study;
- Number and percent of subjects randomized;
- Number and percent of the subjects treated (with at least one dose of study medication);
- Number and percent of the subjects included in each analysis set (as defined in section 4.5).

Following disposition summaries will be based on the Safety Analysis Set (see section 4.5 for analysis sets definition):

- Number and percentage of subject's early discontinuing the study treatment (along with reasons and treatment period of the discontinuation) by sequence.
- Number and percentage of subject's who completed both treatment periods in the study.

4.4.2 Protocol Deviations

A protocol deviation (PD) is any change, divergence or departure from the study design or procedures of a study protocol. Major PDs are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

All PDs will be discussed during a Blinded Data Review Meeting (BDRM) shortly before database lock/ unblinding and addressed with the final classification; as well their overall effect will be evaluated on a subject by subject basis. During the BDRM, all PDs and their possible impacts will be discussed between PAREXEL and the Sponsor and will be assessed as 'Minor' or 'Major'.

The impact of Major PDs on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by Major PDs.

This estimation will be performed at the time of BDRM. Results and population assignments will be summarized in the BDRM report which will be signed off by all relevant scientific experts.

All PDs will be listed by subject in the Safety analysis set as defined in SAP section 4.2.4.

4.5 Analysis Sets

A listing will be presented for inclusion of subjects in each of the below defined analysis sets.
In general, if not otherwise specified, all the efficacy analyses, including primary secondary and explorative, will be executed on:

- FAS, as the primary analysis set
  and
- Completers analysis set for assay sensitivity.

Selected efficacy analyses may be repeated on PPS as an additional robustness analysis.

4.5.1 Safety Analysis Set

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.

4.5.2 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who have taken at least one dose of study medication and provided study baseline and at least one post-baseline primary efficacy variable assessment during the treatment period. The FAS will be used for the primary efficacy analyses.

4.5.3 Completers Analysis Set

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 sensitivity efficacy analyses.

4.5.4 Per Protocol Set

Per Protocol Set (PAS) will consist of all subjects in the completers analysis sets which did not experience any protocol deviations affecting study primary analyses.

4.6 Demographics and Baseline Characteristics

Demographic variables include:

- Birth Year
- Age in Years (as derived in CRF)
- Gender (and, if female the childbearing potential status)
- Race
- Ethnicity

Demographic variables will be listed by subject as defined in SAP section 4.2.4.

Demographic summaries will be based upon the Safety Set as defined in Section 4.5.

Continuous variable of age in years and categorical demographic variables (Gender, Race and Ethnicity) will be summarized descriptively based on Safety analysis set as defined in SAP section 4.2.5.

4.7 DLco

By subject listings of DLco data will be provided as defined in SAP section 4.2.4.

DLco data will be summarized at screening as defined in SAP section 4.2.5.

4.8 Medical History and Concomitant Illnesses

Medical history is assessed at screening and include prior and ongoing medical illnesses and conditions and prior surgical procedures not related to the primary diagnosis.

Medical history summaries will be based upon the Safety Set as defined in Section 4.5.

Medical History terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or later version.

Medical History terms will be listed by subject.

4.9 Prior and Concomitant Medications

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. After screening, prohibited or restricted medications are to be recorded on the corresponding Concomitant Medication eCRF.

Medications will be coded using the World Health Organization Drug Dictionary (WHODD), version global 2019 March B3 or later version and will be presented by Reported Term, WHODD Anatomical-Therapeutic-Chemical (ATC) therapeutic class IV and preferred term (PT).

- Medication start and stop dates will be compared to the dates of IMP intake in both Treatment Periods 1 and 2: Medications that start and stop prior to the date of first of IMP intake in Treatment Period 1 will be classified as prior;
- A therapy is concomitant to the NAL-ER if it started before the date of first NAL-ER intake and stopped on or after the date of first NAL-ER intake or if it started on or after the date of first NAL-ER intake and before the date of last NAL-ER intake.

A therapy is concomitant to the placebo if it started before the date of first placebo intake and stopped on or after the date of first placebo intake or if it started on or after the date of first NAL-ER intake and before the date of last placebo intake.If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication.

Prior and concomitant medications will be listed by subject as defined in SAP section 4.2.4.

Concomitant medications summaries will be based upon the Safety Set as defined in Section 4.5.

Concomitant medications will be tabulated by Anatomical and Therapeutic Class (ATC) of World Health Organization (WHO) drug and preferred term, and as defined in SAP section 4.2.5. Of note: some medications may be concomitant to both treatment arms; these will be duplicated in the corresponding summary table.

Subgroup of patients with prior and concomitant use of anti-fibrotic therapies will be identified based on the review od study medical monitor. Efficacy summaries may be presented in the subgroup of patients with anti-fibrotic therapies as described in the relevant sections of this SAP.

4.10 Treatment Exposure / Compliance

Treatment Exposure and Compliance summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

4.10.1 Treatment Exposure

Extent of exposure will be calculated in days and will be derived separately in the two treatment periods according to treatment received.

Extent of exposure in treatment period (days) = Treatment Period last IMP intake - Treatment Period first IMP intake +1

Extent of exposure will be listed by subject and summarized based on Safety analysis set as defined in SAP sections 4.2.4 and 4.2.5.

4.10.2 Compliance

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.

Compliance, expressed as percent (%), is derived at eCRF level based on the number of tablets actually taken in a particular time interval divided by the number of tablets that should have been taken in that time interval.

Compliance will be assessed at each study visit (on-site or phone visit) via the comparison of reported as not taken or returned blister cards with subject dosing information. The amount of investigational product dispensed and reported as not taken/returned by the subject will be recorded on the drug accountability form at each visit.

Drug accountability variables include:

- Kit Number
- Date Kit Dispensed
- Number of Tablets Dispensed
- Date Kit Returned/ phone visit with reported not-taken kits
- Number of Tablets Returned/Not taken
- Missed doses (Yes/No)
- Number of Tablets Subject was expected to take since last visit
- Number of Tablets Subject actually took since last visit
- Visit Compliance (%) (derived in CRF)

At a visit, each subject compliance status will be classified as follow:

- Compliance < 80%
- Compliance between 80% and 120% (inclusive)
- Compliance > 120%

Drug accountability variables will be listed by subject based on Safety analysis set as defined in SAP section 4.2.4.

Based on Safety analysis set, compliance will be summarized as a continuous variable set as defined in SAP section 4.2.5; as well, compliance status will be summarized as a categorical variable.

4.11 Efficacy Evaluation

All efficacy summaries and analyses will be based upon the FAS as defined in Section 4.5, unless otherwise specified.

4.11.1 Analysis and Data Conventions

4.11.1.1 Multi-center Studies

This is a multicenter, multi-country study.

The statistical model used for assessment of primary endpoint will adjust for site effect.

4.11.1.2 Adjustments for Covariates

The primary efficacy analysis will be adjusted for the following covariates:

1. Subject (random repeated effect)
2. Study baseline measure of primary efficacy variable

4.11.1.3 Handling of Dropouts or Missing Data

Missing or dropout data will not be imputed for the purpose of data analysis.

The Primary Efficacy Analysis will be performed on the FAS and on Completers Analysis Set as sensitivity analysis; there will not be imputation of primary or secondary efficacy endpoints eventually missing at a specific timepoint.

Rules to handle with AEs partial onset and dates will be detailed in section 4.11.1.

4.11.1.4 Multiple Comparisons/Multiplicity

One primary variable has been defined for this study, one critical treatment contrast [NAL-ER vs. Placebo] and one time point of primary interest [Day 22].

Based on the Interim Analysis (IA) look (refer to this SAP at section 4.11.1.5), the study has been interrupted with no sample size adjustment. No alpha adjustment for multiplicity is introduced.

4.11.1.5 Interim Analyses

An interim Analysis has been introduced with Study Protocol, Version 7.0 (December 14, 2021).
Purpose of the IA was to have an early look into selected efficacy results in an unblinded fashion.
Safety results were not part of the IA.
The Conditional Power method was employed to assess study early futility or efficacy.
Based on the IA results, TREVI took decision not to proceed further with this proof of efficacy study. No sample size re assessment has been considered based on IA results.
IA unblinded results were not disclosed to the main blinded team (including Project Leader, Data Management, Biostatistician and Statistical Programmers).
IA unblinded results were visible only to:

- PAREXEL separate unblinded team (including unblinded Biostatistician and unblinded Statistical Programmers);
- TREVI designated unblinded representative.

Strategy to prevent unauthorized disclosure of unblinded information are detailed in the Blinding Maintenance Plan.

4.11.1.6 Examination of Subgroups

Primary endpoint summaries will be produced for gender and anti-fibrotic therapies (defined in section 4.9 of this SAP) subgroups.

As described in section 4.11.3, selected secondary endpoint summaries will be produced for gender and anti-fibrotic therapies subgroups.

4.11.2 Analysis of Primary Efficacy Variable

The primary variable for the assessment of efficacy is presented at section 3.2.1.1 of this SAP.

The primary analysis for the primary endpoint will be on the natural log scale of the daytime cough frequency data. The difference between NAL ER at 162 mg dose level and placebo will be estimated using a mixed-effects model with sequence, period and treatment as fixed effects, the log-transformed study baseline value as a covariate, , and subject as a random repeated effect.

While measurements taken at different time points are expected to correlate, measurements taken at adjacent time points are assumed to be more correlated than measurements further apart, and therefore the compound symmetry covariance structure will be used.

Sensitivity analysis will be conducted with other covariance structures to evaluate the robustness of the compound symmetry structure considered to model the within-subject errors. The following covariance structures will be utilized respectively:

1. Unstructured covariance
2. Heterogeneous Toeplitz
3. Autoregressive AR(1)

A simplified version will be implemented by excluding the site and gender adjustment. The change from study baseline in log-transformed scale (i.e., log-transformed daytime cough frequency at Day 22 – log-transformed study baseline) will be used as the dependent variable.

In the above defined statistical model, the sequence effect can be interpreted as the carry-over effect: hypothesis testing of sequence effect is equivalent to a test of carry-over effect; should sequence results as non-statistically significant, the sequence effect will be removed from the model, knowing that a carryover effect can be excluded.

There will be no imputation for dropouts or missing data for assessments not completed at study visits. In case of no cough registered in the daytime, in order to allow the log transformation 1 cough will be imputed for derivation of daytime cough frequency.

The following SAS code will be used as reference for the described analysis of primary efficacy endpoint:

```
proc mixed;
class SUBJ SEQ PERIOD TRT;
model log (cough Day 22/ baseline) = PERIOD TRT SEQ / cl alpha=0.05 est
solution;
random site / type=cs sub=SUBJ (SEQ);
estimate 'Day 22: Active - Placebo' trt 1 -1 / e cl;
<Add /modify "lsmeans" and "estimate" statements as needed preserving the
model>
run;
```

In the presentation of results, log-scale fitted means at Day 22 will be exponentiated back and percentage changes will be presented in table. A code similar to the below will be used:

```
geomean_perc_change=100*(exp(estimate)-1);
sdrerrback=((logStdErr**2)*((100*(exp(Estimate)))**2))**0.5;
geomean_perc_lowercl=geomean_perc_change-(quantile('NORMAL',
0.975)*sdrerrback);
geomean_perc_uppercl=geomean_perc_change+(quantile('NORMAL',
0.975)*sdrerrback);
```

Where SEQ is study Arm (i.e. Arm 1: NAL-ER + Placebo; Arm 2: Placebo + NAL-ER); Period corresponds to the Study Period; TRT is actual treatment received at the time of the assessment (i.e. NAL-ER; Placebo); SITE is the investigational site.

The above described primary analysis will be executed also on the FAS, as well the same analysis will be repeated on completers as a sensitivity analysis.

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

Following SAS code will be used as reference for the described sensitivity analysis of primary efficacy endpoint:

```
proc glimmix;
class SEQ TRT PERIOD;
model COUGH = TRT BASE DAYTIME SEQ PERIOD dist=negbinomial solution e cl;
random intercept / subject=SITE type=un;
lsmeans TRT / e cl;
estimate 'Day 22: Active - Placebo' trt 1 -1 / e cl;
<Add /modify "lsmeans", "estimate" statements as needed preserving the model>
run;
```

Where SEQUENCE is study Arm (i.e. Arm 1: NAL-ER + Placebo; Arm 2: Placebo + NAL-ER); TRT is actual treatment received at the time of the assessment (i.e. NAL-ER; Placebo); COUGH is number of coughs at timepoint; BASE is the study baseline cough frequency; DAYTIME is duration of daytime (in hours).

A by subject listing will be provided for primary variable as defined in SAP section 4.2.4.

Daytime cough frequency will be summarized by actual treatment received in terms of absolute values and change from study baseline as defined in SAP section 4.2.5. A similar summary table will be produced for gender and anti-fibrotic therapies subgroups, including presentation of stratified means (SAS PROC SURVEYMEANS may be used).

Plots showing the absolute mean change from study baseline in daytime cough frequency by actual treatment received will be provided on both FAS and Completers analysis sets. Similar plots will also be presented by gender and anti-fibrotic therapies subgroups.

From statistical model for primary efficacy endpoint analysis, the geometric mean (GM) for the two treatment and the 95% confidence interval for the GMR and the p-value from the hypothesis test of no difference between the treatment will be presented.

From statistical model for sensitivity analysis of the primary efficacy end point, the 95% confidence interval for the difference between the treatments least squares mean and the p-value from the hypothesis test of no difference between the treatment will be presented.

4.11.3 Analysis of Secondary Efficacy Variables

Secondary efficacy endpoints will be summarized using descriptive statistics except where specified in the subsequent sections.

4.11.3.1 24-hour cough frequency

A by subject listing will be provided for 24-hour cough frequency as defined in SAP section 4.2.4.

24-hour cough frequency will be summarized by actual treatment received and visit in terms of absolute values and changes from study baseline as defined in SAP section 4.2.3. A similar summary table will be produced for gender and anti-fibrotic therapies subgroups, including presentation of stratified means (SAS PROC SURVEYMEANS may be used).

Plots showing the absolute mean change from study baseline in 24-hour cough frequency by actual treatment received will be provided on both FAS and Completers analysis sets. Similar plots will also be presented by gender and anti-fibrotic therapies subgroups.

Natural log transformed 24-hour cough frequency results will be analyzed with mixed-effects model as described for the primary efficacy variable analysis in section 4.10.2; statistical analysis results will similarly be interpreted as described for the primary efficacy variable.

4.11.3.2 This secondary analysis will be executed also on the Completers as a sensitivity analysis. Nighttime cough frequency

A by subject listing will be provided for nighttime cough frequency as defined in SAP section 4.2.4.

Nighttime cough frequency will be summarized by actual treatment received and visit in terms of absolute values and changes from study baseline as defined in SAP section 4.2.3. A similar summary table will be produced for gender and anti-fibrotic therapies subgroups, including presentation of stratified means (SAS PROC SURVEYMEANS may be used).

Natural log transformed nighttime cough frequency results will be analyzed with mixed-effects model as described for the primary efficacy variable analysis in section 4.10.2; statistical analysis results will similarly be interpreted as described for the primary efficacy variable.

This secondary analysis will be executed also on the Completers as a sensitivity analysis.

Plots showing the absolute mean change from study baseline in nighttime cough frequency by actual treatment received will be provided on both FAS and Completers analysis sets. Similar plots will also be presented by gender and anti-fibrotic therapies subgroups.

4.11.3.3 EXACT 14-item e-Diary Tool

A by subject listing will be provided for EXACT 14-item e-Diary Tool scores as defined in SAP section 4.2.4.

EXACT 14-item e-Diary Tool scores results will be summarized by actual treatment received and visit in terms of absolute values and changes from study baseline as defined in SAP section 4.2.3;

a ttest will be used to assess statistically significant difference in the changes from study baseline by actual treatment.

A plot showing the absolute mean change from study baseline by actual treatment received will be provided.

This secondary analysis will be executed also on the Completers as a sensitivity analysis.

4.11.3.4 E-RS diary

E-RS breathlessness (items 7, 8, 9, 10, and 11) and cough items (item 2) will be flagged in the EXACT 14-item e-Diary Tool data listing.

Scores obtained at the E-RS breathlessness scales will be summarized by actual treatment received and visit in terms of absolute values and changes from study baseline as defined in SAP section 4.2.3; a ttest will be used to assess statistically significant difference in the changes from study baseline by actual treatment.

A plot showing the absolute mean change from study baseline by actual treatment received will be provided.

4.11.3.5 This secondary analysis will be executed also on the Completers as a sensitivity analysis. Cough Severity Numerical Rating Scale

A by subject listing will be provided for Cough Severity Numerical Rating Scale as defined in SAP section 4.2.4.

Cough Severity Numerical Rating Scale results will be summarized by actual treatment received and visit in terms of absolute values and changes from study baseline as defined in SAP section 4.2.3.

A plot showing the absolute mean change from study baseline by actual treatment received will be provided.

This secondary analysis will be executed also on the Completers as a sensitivity analysis.

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

A by subject listing will be provided for PROMIS Item Bank v1.0 Fatigue Short Form 7a Scale as defined in SAP section 4.2.4.

Cough Severity Numerical Rating Scale results will be summarized by actual treatment received in terms of absolute values and change from study baseline at Day 21 as defined in SAP section 4.2.5.

A plot showing the absolute mean change from study baseline by actual treatment received will be provided.

This secondary analysis will be executed also on the Completers as a sensitivity analysis.

4.11.3.7 CGI-C

A by subject listing will be provided for CGI-C as defined in SAP section 4.2.4.

CGI-C results will be summarized based on FAS by actual treatment received in terms of absolute values and change from study baseline at Day 21 as defined in SAP section 4.2.5.

A boxplot showing the mean CGI-C by actual treatment received will be provided.

This secondary analysis will be executed also on the Completers as a sensitivity analysis.

4.11.4 Pharmacokinetics

4.11.4.1 Pharmacokinetic Concentrations

Pharmacokinetic plasma concentration of nalbuphine (parent and metabolites), will be listed in Separately set according to SAP section 4.2.4. Listings will include actual sampling times relative to dose administration. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as Below Limit of Quantification (BLQ) in the listings.

Plasma concentrations of nalbuphine (parent and metabolites) will be summarized by nominal timepoint and as defined in SAP section 4.2.5. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV%=SQRT(e^{s^2}-1)*100; where s is the standard deviation of the log-transformed values), median, minimum and maximum values.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- Source data shall be used in all derived PK concentrations without prior rounding
- The mean, standard deviation (SD), geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.
- Geometric coefficient of variation (CV) % and coefficient of variation (CV%) will be presented to one decimal place.

4.11.4.2 Handling of Values Below the Limit of Quantification (BLQ)

All concentrations BLQ or missing data will be labeled as such in the concentration data listings.

Missing samples will be reported as no sample ("NS") and excluded from analysis.

In summary tables, all BLQ values will be set to the ½*lower limit of quantification (LLOQ), and all descriptive statistics will be calculated.

The number of BLQ values will be reported for each time point

4.11.4.3 Pharmacokinetic Parameters

Not Applicable

4.11.4.4 Pharmacokinetic 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.

4.11.5 Additional Exploratory Efficacy Evaluation

Responder analysis assessing 30%, 50% and 75% reduction in daytime cough counts

Exploratory variable described in this SAP section 3.2.4

4.12 Number and percentages of subjects with 30%, 50% and 75% reduction from baseline in daytime cough counts will be listed and presented by treatment group. Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.5.

4.12.1 Adverse Events

4.12.1.1 Definition of Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a clinical investigation subject reported on or after the first screening date, which does not necessarily have a causal relationship with this treatment. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.

4.12.1.2 Definition of Treatment Emergent Adverse Event (TEAE)

A TEAE is an AE occurring on or after the initial administration of investigational product. In this study, AEs may be treatment emergent with respect to treatment assumed in treatment period 1 or treatment period 2. The following will apply:

- AEs with onset date prior to the date of first of IMP intake in Treatment Period 1 will be considered as AEs non treatment emergent.
- AEs with onset date on or after the date of first IMP intake in Treatment Period 1 (but before first IMP intake in Treatment Period 2) will be considered as Treatment Period 1 TEAE.
- AEs with onset date on or after the date of first IMP intake in Treatment Period 2 will be considered as Treatment Period 2 TEAE.

4.12.1.3 Definition of Serious Adverse Event (SAE)

AEs fall into the categories “non-serious” and “serious.”.

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

4.12.1.4 Severity

All AEs will be graded for severity, if possible, by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or later.

4.12.1.5 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".

AEs with causal relationship to IMP "definitely related", "probably related", "possibly related" will be considered as 'Related' AEs; AEs with causal relationship to IMP "unlikely related", or "not related" will be considered as 'Not Related' AEs

4.12.1.6 Adverse Event of Special Interest (AESI)

Certain adverse events, spontaneously reported by a subject, will be documented in more detail as part of the analysis to determine any abuse potential of nalbuphine.

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

- Additional Subject's Narrative, i.e. a description of the AE event in the subject's own words;
- Investigator comments and/or assessment;
- 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); such an estimate is directly collected from eCRF;
- Prior history of this symptom or event.

4.12.1.7 Handling of AEs partial dates

If medication start date is missing or partial, the dates will be compared as far as possible with the date of first dose of study medication in both Treatment Periods to assess if the AE is treatment emergent with respect to one of the two treatment periods.

4.12.1.8 Analysis of AEs

All AEs will be listed as defined in SAP section 4.2.4. The following information will be included in the listings: Description of AE, System Organ Class (SOC), Preferred Term, onset date, end date, TEAE status, CTCAE Severity Grade, Seriousness (Yes/No and seriousness criteria), Outcome, Relationship to Study Treatment, Action Taken with Study Treatment, Other Actions Taken, AE of Special Interest (Yes/No).

All AESI will be listed separately following definition in SAP section 4.2.4. The following information will be included in the listings: Description of AE, System Organ Class (SOC), Preferred Term, onset date, end date, TEAE status, AE of Special Interest (Yes/No), Subject's Narrative, Investigator's Comments, onset datetime, estimated time between last dose and onset of AESI, prior history of the symptom or event.

The TEAEs will be presented using summary tables as defined in SAP section 4.2.5, in general, in TEAEs summaries number of subjects with an event will be printed as well as number of events.

Summary tables:

- Patient Overall Summary of TEAEs; this table will include following summaries:
    - Any TEAEs

- Any related TEAEs
- Any Serious TEAEs
- Any related Serious TEAEs
- Any treatment emergent AESIs
- Any related treatment emergent AESIs
- Any serious treatment emergent AESIs
- Any related serious treatment emergent AESIs
- Any Grade 3 or higher TEAEs
- Any Related Grade 3 or higher TEAEs
- Any TEAEs leading to IMP interruption
- Any Related TEAEs leading to IMP interruption
- Any TEAEs leading to IMP withdrawn
- Any Related TEAEs leading to IMP withdrawn
- Any FATAL TEAEs
- Any Related FATAL TEAEs

- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- TEAEs by SOC and PT and Worst CTCAE Grade
- Related TEAEs by SOC and PT and Worst CTCAE Grade
- Serious TEAEs by SOC and PT
- Related Serious TEAEs by SOC and PT
- TEAEs Leading to IMP interruption by SOC and PT
- Related TEAEs Leading to IMP interruption by SOC and PT
- TEAEs Leading to IMP withdrawn by SOC and PT
- Related TEAEs Leading to IMP withdrawn by SOC and PT
- Fatal TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- Serious AEs – Key Subject Information
- Adverse Events with Outcome of Death – Key Patient Information

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or higher.

4.12.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Reporting of Deaths, Serious Adverse Events and other significant Adverse Events is described in the above section 4.11.1.1.

4.12.3 Clinical Laboratory Evaluation

By subject listings of safety laboratory data will be provided as defined in SAP section 4.2.4. Abnormal safety laboratory data will also be listed separately.

4.12.4 Safety laboratory data will be summarized by actual treatment received and visit as defined in SAP section 4.2.5. Pregnancy

Pregnancy test results will be listed as defined in SAP section 4.2.4.

4.12.5 Vital Signs

By subject listings of vital signs will be provided as defined in SAP section 4.2.4.

Vital signs will be summarized by actual treatment received and visit as defined in SAP section 4.2.5.

4.12.6 Physical Examination

By subject listings of Physical Examination will be provided as defined in SAP section 4.2.4.

4.12.7 ECG

By subject listings of ECG data will be provided as defined in SAP section 4.2.4.

ECG data will be summarized by actual treatment received and visit as defined in SAP section 4.2.5.

4.12.8 Spirometry

Spirometry will not be executed at the end of treatment period 1 (Visit 6), therefore the screening spirometry results will be used as study baseline for both period 1 and period 2.

By subject listings of Spirometry results will be provided as defined in SAP section 4.2.4.

Spirometry results will be summarized by actual treatment received and visit as defined in SAP section 4.2.5.

4.12.9 Swallow Test

By subject listings of Swallow Test data will be provided as defined in SAP section 4.2.4.

4.12.10 SOWS

By subject listings of SOWS results will be provided as defined in SAP section 4.2.4.

SOWS results will be summarized by actual treatment received and study day as defined in SAP section 4.2.5.

4.12.11 Data Safety Monitoring Board (DSMB)

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.

4.13 Other Analyses

Not Applicable

4.14 Determination of Sample Size

Original Sample size assumptions

The planned sample size of 44 subjects (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.

Study early interruption

As described in this SAP at sections 4.11.1.5 and 4.15, study was terminated before reaching the total sample size.

4.15 Changes in the Conduct of the Study or Planned Analysis

Following an Interim Analysis, the study recruitment was terminated with the last eligible subjects enrolled/randomized on or before 11MAR2022.

Additional exploratory analysis re added in this SAP, prior than study general unblind.

5 REFERENCES

[1] ICH HARMONISED TRIPARTITE GUIDELINE, STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS, E3, 30 November 1995 (https://www.ich.org/page/efficacy-guidelines)

[2] ICH HARMONISED TRIPARTITE GUIDELINE, STATISTICAL PRINCIPLES FOR CLINICAL TRIALS, E9, 5 February 1998 (https://www.ich.org/page/efficacy-guidelines)

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[4] Bacci ED, O'Quinn S, Leidy NK, Murray L, Vernon M. Evaluation of a respiratory symptom diary for clinical studies of idiopathic pulmonary fibrosis. Respir Med. 2018 Jan;134:130-138.

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6 APPENDICES

6.1 Schedule of Assessments

Appendix 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.

Appendix 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.

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