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

NCT Number: NCT05962151

Document Date: Protocol Amendment 2 : 19 June 2024

CLINICAL TRIAL PROTOCOL: NAL04-201

Study Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Period Crossover Efficacy and Safety Study of Nalbuphine ER Tablets for the Treatment of Refractory Chronic Cough
Short Study Title	Cough Reduction in RCC with NAL ER (RIVER)
Study Number:	NAL04-201
Study Phase:	2
Product Name:	Nalbuphine Extended-Release Tablets (NAL ER)
Reference Number/s:	N/A
Indication:	Refractory Chronic Cough
Investigators:	Multicenter
Sponsor:	Trevi Therapeutics, Inc. 195 Church Street, 16th Floor New Haven, CT 06510, USA
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted], MD
Protocol Version	**Protocol Amendment 2 19-Jun-2024**
Amendment Scope	Global protocol revision including all country-specific amendments, and additional global changes

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator, potential Investigator or consultant for review by you, your staff and applicable Independent Ethics Committee and/ or Institutional review Board.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Date
Protocol Amendment 2	*19-Jun-2024*
Protocol Amendment 1a-UK	*24-Oct-2023*
Protocol Amendment 1	*7-Aug-2023*
Original Protocol	*27-Jun-2023*

AMENDMENT 2 19-JUN-2024

Overall Rationale for the Amendment: Protocol Amendment 2 was created to align local amendments into one global unified Protocol Amendment, and clarify the changes detailed below:

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
Synopsis and SoE	Align the synopsis and SoE with the body of the protocol. See the applicable section for details and rationale for the updates in the synopsis SoE.	Administrative
List of Abbreviations	Added EOS, FU, IUS, PP, SoE, and TdP, corrected or removed abbreviations. Terms with © or ® are marked at important points in the text, and symbols removed from the rest of the text.	Administrative
Throughout Protocol	Added text "*End of Study" or "EOS*" to reference to the "Safety Follow-up" or "FU" visit.	Clarify End of Study (EOS) for the subject
2.1 and 2.2 Background on RCC and Nalbuphine	Added clarifications on definition of RCC, and availability of NAL ER in Europe.	Add detail for clarity
2.4 Rationale for Study Design	Added text "*The use of placebo as a comparator is justified for this study due to ...."*	Clarify alternative therapies and rationale for use of placebo
2.5 Risk/Benefit and Ethical Assessment	Added paragraph starting and ending with the below text: "*The TR12 study in patients with IPF-associated chronic cough demonstrated ... dose level, so the maximal dose in the current RIVER study is 108 mg BID."*	Increase detail on the dose justification
3.2 Secondary Objectives	Patient and Clinical Global Assessments – Separated endpoint for assessment of change, as it is not done at baseline.	Correct the endpoint to match the use of the tool
4.1 Study Duration and Dates	Added text "*The overall end of study is defined as the last study visit for the last patient (LPLV)*"	Clarify EOS for the overall study
4.1 Study Duration and Dates	Added text "*Following their participation in the study, subjects will return to the care of their usual physician for the continued management of their condition or, if needed, they will be referred to appropriate care."*	Define subject return to routine care at the end of the study
4.2 Overall Study Design and plan	Removed requirement for follow up at planned end of study in case of early discontinuation	Not required for Phase 2a study

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
5.2 Inclusion Criteria	#1 – added "*Current*" and "*and history of chronic cough*" #2 – added "*and after onsent of chronic cough*" #5 – corrected FEV1/FVC to the ratio	Added detail to correct and clarify
5.3 Exclusion Criteria	#3 - added "*or other significant respiratory disorder that might effect cough*" #7 Cardiac Safety: corrected criteria to differentiate correctly the QRS in regular subjects vs those with RBBB #13 – added "*as assessed by the investigator*" #23 – added "*baclofen, tricyclics*" #24 – clarify reason for ACE inhibitor exclusion #25 – add example of cough suppressants	Added detail to correct and clarify
5.3 Exclusion Criteria	#26 – new criteria: "*Medications prescribed for asthma, rhinitis/upper airway cough syndrome, or gastroesophageal reflux disease are prohibited unless on a stable dose for 14-days prior to the baseline visit and are expected to remain at that dose for the duration of the study*"	Stabilize confounding medications that could impact the endpoint.
6.5 Multiple Missed Doses	Changed 6 missed doses (approx. 3 days) to 3 missed doses (approx. 1.5 days) as the threshold for discussion with the study Medical Monitor/s	Facilitate Medical Monitor contact at an earlier timepoint
7.2 Reporting of Adverse Events	Added text "*Clinically relevant findings on ECG, laboratory testing, or physical examination during Screening* *…* *the Adverse Event eCRF*." To replace the text "*Clinically significant findings noted prior to the start of investigational product treatment will be recorded as medical history*".	Add detail for clarity
7.2.2 Adverse Events Requiring Additional Narratives	Added the terms: *Dissociation, Feeling drunk* and *Hallucinations (any)* Revised the terms: *Polysubstance dependence* to *Substance dependence*, *Intentional drug misuse* to *Intentional product misuse, Elevated Mood to Euphoric mood*	Revisions due to MedDRA updates and Sponsor Decision
7.2.4 Severity Grading	Updated the section title	Add detail for clarity
7.4 Pregnancy	Clarified procedures in case of pregnancy, and updated that the outcome of the pregnancy will be followed up no *later* than 6-8 weeks following estimated due date	Update for clarity
8.4 Subject Symptom and Medication Logs and 8.6 Concomitant Medication and Therapy Assessments	Added text for Symptom Log that "*new and/or changed*" items should be recorded. Added text for the Medication Log that the addition, change, or discontinuation of "*medications, therapies, including oxygen therapy, over-the-counter (OTC) medications, herbal medications, vitamins, and nutritional supplements will be reported*" Added text that the logs will be "*reviewed by staff and applicable information entered in eCRF*"	Clarify how the subject logs should be used

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
8.6.1 Prohibited and Restricted Medications, and Washout Including Table 7	Clarified implications for study withdrawal of taking restricted medication, and defined stable dose. Table 7 updated table to align with the medication exclusion criteria, and for consistency	Added detail for clarity, and update for consistency
8.9 Electrocardiogram (ECG)	Added text "*will be assessed by the ECG specialist vendor and a report sent to site within 72 hours of successful transmission.* *The screening ECG central read report will be used for the purpose of meeting the ECG study inclusion criteria"*	Added detail for clarity
8.11 Clinical Laboratory Tests	Added text "*Once processed, samples will be stored for an interim period at the site before shipping to the location where the analysis will be performed. Once at the analysis location, after analysis, samples can be stored for up to 1 month, before being destroyed."* *"at the central lab using consistent methodology and procedures globally at the testing locations (ICON Laboratories in Ireland and US)"* Clarified that only the Urine Pregnancy Test is tested locally at site.	Define the testing, storage time and location of routine lab samples
8.12 Blood Sampling for Pharmacokinetics (PK)	Added text "*Once processed, samples will be stored for an interim period at the site, before shipping to the central lab for forwarding to the PK lab. Samples that are sent to the PK lab can be stored for up to 5 years in case of the need for retesting for this study before being destroyed."*	Define the storage time and location of PK lab samples
8.13 WOCBP Pregnancy test, and contraceptive counselling	Added text "*without an alternative medical or medication cause (e.g. hormonal treatments)*" and "*Permanently*", and expanded on definition of permanently sterile, for definition of non-WOCBP. Added text "*Intrauterine hormone-releasing system (IUS)*", as acceptable method of birth control.	Align with Clinical Trials Facilitation & Coordination Group (CTFG) Guidance
8.15 24-hour Digital Cough Monitor	Added text about the measures taken to preserve privacy: "*The recording is encrypted on the device and transferred electronically to the UK via a secure web portal*." And "*by specially trained individuals working under strict SOPs to ensure confidentiality* *…* *do not have access to listen to the records*"	Add detail for clarity
8.16 Patient Reported Outcomes (PRO) Questionnaires	Clarifications on Tools and timing of the PROs	Add detail for clarity
8.16.1 SOWS (Subjective Opiate Withdrawal Scale), and PRO SoE Footnotes	Added text "*Subject reported symptoms of withdrawal captured on the SOWS will not be reported as an Adverse Event unless reported verbally as part of the overall AE assessment at each visit*", to replace text requiring reporting of SOWS answers as Medical History or Adverse Events.	Correct the documentation of SOWS PRO answers
8.21 Tolerance and Titration Symptoms Management	Added text about consultation with the medical monitor in case of missed doses or continued lack of tolerance.	Increase medical monitor contact
8.22 Premature Discontinuation	Clarified the protocol allowed reasons for discontinuation from the study.	Facilitate Medical Monitor real-time

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
	Added text "*Subjects have the right to discontinue … discontinuation has occurred.*" Clarified the steps to be taken if a subject permanently discontinues the study drug. Added the text that "*the last study procedure or visit under the subject's consent will be considered End of Study*"	awareness of premature discontinuations Add detail for clarity
8.23 Appropriateness of Measurements	Added detail about use of the VitaloJAK and e-diary	Add detail for clarity
9.5 Analysis Populations	Added text "*Per Protocol (PP) population: The PP population will consist of all subjects in the mITT population who have a treatment compliance >80% during the fixed dose period and do not have a protocol deviation that excludes subjects from the PP population. A complete list of protocol deviations that will exclude subjects from the PP population will be provided in the SAP. Subjects who are withdrawn from the study by the sponsor due to a deviation (see Section 10.9) will be excluded from the PP population*"	Increase detail on the per protocol population
10.1 Quality Control and Assurance	Changed "should" to "will" for Investigator responsibilities.	Make investigator responsibility compulsory
10.6 Patient Confidentiality and Data Protection	Added text to this section: "*(e.g., from the e-diary, cough monitor, labs)"* *"(pseudonymized)"* *"This code list will remain on site and kept in a secure manner with the study documentation, with access limited to authorized individuals."* *"Identifiable (non- pseudonymized) personal study-related data will be accessed by the sponsor … used in this way to participate in the study."* *"The compliance with these requirements is confirmed and documented throughout … data transfer agreements and quality agreements, where appropriate."* *"In case of security breach procedures for reporting and disclosure within the regulations and timelines of the applicable countries for the study will be followed."* The above text replaced and expanded upon the below deleted text: *"The level of disclosure will be explained to the subject who will be required to give consent for their data to be used as described in the informed consent"*	Increase detail on the data protection processes
10.9 Protocol Violations/Deviations	Changed "*not evaluable*" to "*ineligible for inclusion in the per protocol population*"	

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
10.11 Data Generation and Analysis	Added text "*The data generated to answer the objectives of the study are:* *…* *and no data is recorded in the eCRF directly. Data will be*" And "*The following data is generated by the subject or by a vendor,* *…* *source of the actions and results themselves will be the vendor database.*"	Clarify data collected, and the location of the source data
10.12 Retention of Data	Replaced text "*as long as needed*" with "*25 years*" Deleted "*and sponsor requirements*" and added "*before destroying the data*"	Clarify data retention time and destruction
10.14 Publication and Disclosure Policy	Added text *"The results of the study will be posted to the publicly accessible website ClinicalTrials.gov independent of the outcome of the study.*	Clarify disclosure of results
11 References and throughout	Added new references, and removed references no longer applicable. Corrected, added, or aligned in-text references throughout where required.	Administrative

AMENDMENT 1: 7-AUGUST-2023

Overall Rationale for the Amendment:

Protocol Amendment 1 was created to clarify exclusion criteria and restricted medications as follows:

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
Synopsis Exclusion Criteria/Section 5.3 Exclusion Criteria	Addition of exclusion regarding a subject's hypersensitivity to nalbuphine or NAL ER excipients.	IB section 6.4 "Contraindications" indicates that Nalbuphine ER tablets should not be used in subjects with a hypersensitivity to nalbuphine or to any of the other ingredients in NAL ER tablets.
Synopsis Exclusion Criteria and Section 5.3 Exclusion Criteria	Addition of exclusion regarding language defining use of Known Risk Drugs.	IB section 6.7 indicates that because a formal TQT study has not been conducted for NAL ER, concomitant use of medications classified as having a known risk for Torsade des Pointes should not be used concomitantly.
Section 8.6.1 Table 7 Prohibited and Restricted Medications, and Washout	Addition of the use medication having known risk of Torsades de Pointe (categorized as KR on the Credible Meds® website Medications associated with a potential risk of QT prolongation, but not clearly associated with Torsade de Pointes.	Explanation of restriction and washout period

1. PROTOCOL SYNOPSIS

1.1. Synopsis

Name of Sponsor/Company: Trevi Therapeutics, Inc.	**Study Number:** NAL04-201	**Protocol Amendment 2**
Name of Finished Product: Nalbuphine Extended-Release Tablets (NAL ER)		
Name of Active Ingredient: nalbuphine hydrochloride (HCl)		
Title of Study: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Period Crossover Efficacy and Safety Study of Nalbuphine ER Tablets for the Treatment of Refractory Chronic Cough		
Short Study Title: Cough Reduction in RCC with NAL ER (RIVER)		
Study Phase: Phase 2	**Study Centers:** Approximately 12-16 centers	**Protocol Amendment 2** 19-Jun -2024
Planned Study Period: 2023-2024	**Duration of Treatment per subject:** 21 Days per Treatment Period	**Duration of Study per subject:** up to 15 Weeks
Number of Subjects: Approximately 60 subjects diagnosed with RCC will be randomized to ensure evaluable data from at least 48 subjects who complete both treatment periods.		

Study Objectives and Efficacy Endpoints:

Objective	Endpoint
Primary Objective	
Effect of treatment on 24-hour cough frequency (coughs per hour) after 21 days	• Relative change from Baseline in 24-hour cough frequency (coughs per hour) as assessed by objective cough monitoring at Day 21 for NAL ER compared with placebo.
Secondary Objectives	
Safety and tolerability of NAL ER for the treatment of Refractory Chronic Cough (RCC)	• Adverse events, clinical laboratory assessments, vital signs, and physical examination summaries. • ECG summaries [ECGs will be analyzed in a separate report]. • Subjective Opiate Withdrawal Scale (SOWS) daily summaries for the 14 days following the last dose of investigational product.
24-hour cough frequency (Coughs per hour)	• Relative change from Baseline in 24-hour cough frequency (coughs per hour) at Days 7 and 14 for NAL ER compared with placebo. • Proportion of responders with ≥30%, ≥50% and ≥75% reduction in the 24-hour cough frequency at Days 7, 14, and 21 for NAL ER compared with placebo.
Awake cough frequency (Coughs per hour)	• Relative change from Baseline in awake cough frequency (coughs per hour) at Days 7, 14, and 21 for NAL ER compared with placebo.
Sleep cough frequency (Coughs per hour)	• Relative change from Baseline in sleep cough frequency (coughs per hour) at Days 7, 14, and 21 for NAL ER compared with placebo.
CS-VAS (Cough Severity Visual Analogue Scale)	• Change from Baseline in the Cough Severity Visual Analogue Scale at Days 7, 14, and 21 for NAL ER compared with placebo.

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LCQ© (Leicester Cough Questionnaire)	• Change from Baseline in the LCQ total score at Day 21 for NAL ER compared with placebo.	
Patient-Reported Cough Frequency (PR-CF)	• Change from Baseline in the PR-CF at Days 7, 14, and 21, for NAL ER compared with placebo. • Proportion of PR-CF responders, with response defined as at least a one category improvement at Days 7, 14, and 21 for NAL ER compared with placebo.	
PGI-S, PGI-C, Cough (Patient Global Impression of Severity and Change for Cough)	• Change from Baseline in the PGI-S Cough at Days 7, 14, and 21 for NAL ER compared with placebo. • PGI-C Cough score at Days 7, 14, and 21 for NAL ER compared with placebo.	
CGI-S, CGI-C, Cough (Clinical Global Impression of Severity and Change for Cough)	• Change from Baseline in the CGI-S Cough at Day 21 for NAL ER compared with placebo. • CGI-C Cough score at Day 21 for NAL ER compared with placebo.	

Pharmacokinetics: Nalbuphine (and/or metabolites) plasma concentration will be measured for each treatment group at all visits where subject is on treatment. A PK sample will be drawn and correlated with the time of IP intake as reported by the subject.

Study Design:

A double-blind, randomized, placebo-controlled, 2-period crossover study for the treatment of cough in subjects with Refractory Chronic Cough.

Based on the screening cough monitor results, the study will enroll subjects in a 1:1 ratio to subgroups of 10-19 coughs/hour and ≥20 coughs/hour.

After meeting eligibility during the screening period, subjects will be randomly assigned (1:1) to one of the following sequences:

- NAL ER in Treatment Period 1, followed by Placebo (PBO) in Treatment Period 2
  OR
- PBO in Treatment Period 1, followed by NAL ER in Treatment Period 2

The 21-day treatment periods are separated by a 21-day washout period. NAL ER will be titrated according to the *Table: Dosing Scheme*.

Study visits in each treatment period will be at Day -1 for Baseline cough assessments, and at Days 6, 13, and 20. Visits and Assessments are described in *Figure: Study Schematic*, and *Section 1.2 Schedule of Events, Table 1 and Table 2*. Subjects will have blood drawn for pharmacokinetic (PK) analysis of nalbuphine plasma concentration. Subjects will also complete questionnaires for efficacy evaluations and undergo safety evaluations including an electrocardiogram (ECG).

At the Screening and Baseline visits and on Days 6, 13, and 20 during each treatment period, site staff will place an electronic cough monitor on the subject, which will be worn for a 24-hour recording period to assess cough frequency. At the end of each recording session (Days 7, 14, and 21), the monitor will be removed at home by the subject, and the subjects will complete Patient Reported Outcomes (PROs) questionnaires in the diary. The monitor will be returned to the clinical study center for processing.

Subjects will be taken off study drug at the end of the Treatment Period 2 and followed off treatment for an additional 2 weeks.

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If permanent discontinuation of investigational product occurs the discontinuation and safety follow-up (FU)/end of study (EOS) visits should be performed. End of Study for any participant will occur when the safety follow-up visit is completed,14+3 days after last dose, or withdrawal of consent.

Figure: Study Schematic

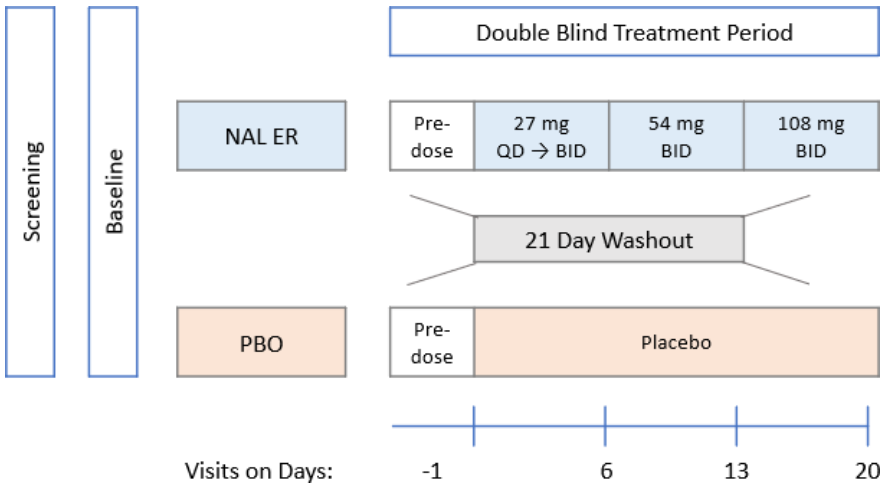

Table: NAL ER Dosing Scheme

Grey shading indicates cough monitor application and recording period.

VISIT	Study Day (TP1 or TP2)	NAL ER Dose (mg)		PLACEBO (PBO)	
		AM	PM	AM	PM
Baseline	-1	—	—	—	—
	1	—	27	—	PBO
	2	—	27	—	PBO
	3	27	27	PBO	PBO
	4	27	27	PBO	PBO
	5	27	27	PBO	PBO
Day 6	6	27	27	PBO	PBO
	7	27	54	PBO	PBO
	8	54	54	PBO	PBO
	9	54	54	PBO	PBO
	10	54	54	PBO	PBO
	11	54	54	PBO	PBO
	12	54	54	PBO	PBO
Day 13	13	54	54	PBO	PBO
	14	54	108	PBO	PBO
	15	108	108	PBO	PBO
	16	108	108	PBO	PBO
	17	108	108	PBO	PBO
	18	108	108	PBO	PBO
	19	108	108	PBO	PBO
Day 20	20	108	108	PBO	PBO
	21	108	—	PBO	—

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Study Population:

Inclusion Criteria

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

1. Current **diagnosis of refractory chronic cough** (RCC); and history of cough for at least one year. Defined in the ERS Guidelines as chronic cough that is refractory to conventional treatment of cough-associated conditions or where no cough-associated conditions can be identified (*Morice et al, 2020*).
2. **Chest radiograph or computed tomography (CT)** of the thorax performed within the last 24 months and after the onset of chronic cough or during the screening period not demonstrating any abnormality considered to be significantly contributing to the refractory chronic cough in the opinion of the Principal Investigator.
3. Score of **≥40mm on the Cough Severity VAS** at the Screening visit.
4. 24-hour objective **cough frequency ≥10 or ≥20 coughs/hour** based on cough monitor recording performed during the Screening Period, with results reviewed prior to baseline visit. Study will enroll subjects in a 1:1 ratio to subgroups of 10-19 coughs/hour and ≥20 coughs/hour.
5. **FEV1 / FVC ratio ≥ 60%** as determined by spirometry adhering to ATS/ERS guidelines. (*Graham et al, 2019*).
6. Males or females ages 18 years and older at the time of consent.
7. Willing and able to provide written informed consent, comply with study requirements and restrictions, and 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. Clinical diagnosis of **sleep apnea** and/or use of CPAP.
2. Upper or lower **respiratory tract infection** or change in pulmonary status in the last 6 weeks prior to the baseline visit.
3. History of **bronchiectasis, chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF),** or other significant respiratory disorder that might affect cough**.**
4. History of **uncontrolled asthma**.
5. Current **smokers/vapers**, individuals who have given up smoking ≤12 months, individuals using nicotine patches, gum, or any other nicotine supplements, or individuals with a smoking history of 20 pack-years or more.
6. **Speech therapy/physiotherapy for RCC** is acceptable if the subject has started the therapy at least 4 weeks prior to the Baseline visit and continues the therapy through the Treatment Periods. It may not be started within 4 weeks of starting the study or for the duration of the study.
7. **Cardiac Safety:** Mean QTcF value of 3 centrally read screening Electrocardiograms (ECG) calculated as
   a) ≥470ms if QRS <120ms or
   b) ≥500ms in the presence of either a Right Bundle Branch Block (RBBB) or QRS≥120ms
8. **Heart Rate** <50 bpm or >100 bpm, as determined by vital signs pulse obtained over 30-60 seconds
   a) Subjects with a resting heart rate of <50 bpm will have it repeated once after 5 minutes in the supine position, and if it remains <50 bpm during the repeat, they will be considered a screen failure.

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b) Subjects with a rate >100 bpm should be considered a screen failure. Rescreening may be possible with the approval of the medical monitor, after medical or alternative management of the atrial fibrillation.

9. **Kidney Function**: Estimated glomerular filtration rate ≤ 44 mL/min/1.73 m^2 at Screening.
10. **Liver Function**: Total Bilirubin >3mg/dl [>50umol/L] and Serum Albumin <2.8g/dl
11. History of 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.
12. History of **substance abuse** including excessive alcohol consumption, that in the opinion of the Investigator, may interfere with the conduct of the study.

    Alcohol consumption should be limited for the duration of study treatment.
13. **Significant medical condition** or other factors as assessed by the investigator that may interfere with the subject's ability to successfully complete the study.
14. **Pregnant or lactating female subject**. Women of childbearing potential (WOCBP) must use an acceptable method of birth control and have a negative pregnancy test at the screening and baseline visits. WOCBP and acceptable methods of birth control are defined in the protocol,

    Section 8.13 Pregnancy test, and contraceptive councelling.
15. Known **intolerance** (gastrointestinal, central nervous system symptoms), hypersensitivity, drug allergy following the use of an opioid drug.
16. Known hypersensitivity to nalbuphine or to NAL ER excipients.
17. Previous enrollment in a NAL ER clinical study.
18. Concurrent enrollment in an **ongoing clinical trial** or anticipated enrollment in a concurrent clinical trial. Observational or long-term safety follow-up studies (e.g., in a vaccine study) may be allowed upon medical monitor approval.

Medication-related Exclusions:

(Refer to protocol *Section 8.61 Prohibited and Restricted Medications, and Washout*):

19. Use of **opiates** is prohibited within 14 days prior to the baseline visit. Includes opiate-containing anti-cough agents, and naltrexone. Subjects are prohibited from using opioids for the duration of the study.
20. Use of **benzodiazepines** are prohibited within 14 days prior to the baseline visit and for the duration of the study.
21. **Monoamine oxidase inhibitors** (MAOIs) including methylene blue (methylthioninium chloride) and the antibiotic linezolid are prohibited within 14 days prior to the baseline visit and for the duration of the study.
22. Exposure to any **investigational medication**, including placebo, is prohibited within 4 weeks prior to the baseline visit and for the duration of the study.
23. Use of **pregabalin, gabapentin, baclofen, tricyclics, or thalidomide** given for the treatment of cough is prohibited within 14 days of the Baseline visit, and for the duration of the study.

    Pregabalin, gabapentin, baclofen, tricyclics, or thalidomide required for other indications, is permitted if on a stable dose for at least 4 weeks, and still experiencing significant cough, and expected to remain on that dose for the duration of the study.
24. Use of **ACE inhibitors** is prohibited within 12 weeks prior to the baseline visit, and for the duration of the study (due to potential for causing cough).

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25. Other medications prescribed as **cough suppressants** (such as dextromethorphan or benzonotate) are prohibited unless on a stable dose 14-days prior to the baseline visit and are expected to remain on that dose for the duration of the study.
26. Medications prescribed for **asthma, rhinitis/upper airway cough syndrome, or gastroesophageal reflux** disease are prohibited unless on a stable dose for 14-days prior to the baseline visit and are expected to remain at that dose for the duration of the study.
27. Use of **medications that affect serotonergic neurotransmission** and that when used concomitantly with opioids can cause serotonin syndrome are prohibited unless on a stable dose for 14-days prior to the baseline visit and are expected to remain on that dose for the duration of the study.
28. **Strong inhibitors/inducers of the P450 Isozymes** are prohibited unless on a stable dose for 14-days prior to baseline visit and are expected to remain on that dose for the duration of the study.
29. Use of a medication having a "known risk" of Torsade de Pointes (TdP) (categorized as "KR" on the *Credible Meds® website*) is prohibited at entry or during the study. Medications associated with a potential risk of QT prolongation, but not clearly associated with TdP, 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 baseline.
    - 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.

Statistical Methods:

Efficacy

The primary efficacy endpoint of relative change in 24-hour cough frequency (coughs per hour) will be analyzed using a mixed-effects repeated model. This model will use log-transformed relative change in 24-hour cough frequency (log (Timepoint/ Baseline)) as the response with sequence, treatment, and time as fixed effects, the log-transformed baseline 24-hour cough frequency and sex as covariates, 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. In the presentation of results, log-scale fitted mean treatment group differences at Day 21 will be back-transformed to fitted ratios of geometric means.

As a supplementary analysis, a negative binomial model will be fitted with the number of coughs as the outcome, with terms for sequence, treatment, time, baseline cough frequency with subject as a random effect.

The primary efficacy analysis and secondary analyses that require comparison of placebo and NAL ER will be analyzed using the population of subjects for whom baseline and Day 21 measurements are non-missing for both periods. Summaries by treatment will consist of all subjects with a baseline and Day 21 measurement for that treatment, unless evidence suggests a sequence effect, in which case summaries will be presented by treatment and sequence.

Safety

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 laboratory data, physical examinations, and SOWS 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.

Additional descriptive narratives will be collected for relevant adverse events to support an eight-factor analysis.

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ECGs will be reviewed locally for safety. ECGs will be read centrally by specially trained staff and 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 specialist vendor.

Pharmacokinetics

Nalbuphine (parent and/or metabolites) plasma concentration data will be listed by collection time and nalbuphine dose where applicable. Additional PK-PD analysis may be conducted if data allows and will be presented in an ad-hoc report.

Sample Size and Power

Assuming that subjects on placebo will experience a mean 20% reduction in 24-hour cough frequency from baseline to Day 21 and subjects on NAL ER will experience a mean 45% reduction from baseline to Day 21, the planned sample size of 48 subjects (24 per sequence) provides at least 80% power to detect a significant difference between NAL ER treatment and placebo at the 5% significance level (2-sided). This assumes a coefficient of variation (CV) of 1.12 in log-transformed Day 21 cough frequencies which is the CV estimated from *Kelsall et al (2011)* data on chronic cough in patients without esophageal catheterization.

A total of approximately 60 subjects will be randomized to ensure complete data from at least 48 subjects, assuming a ~20% dropout rate.

1.2. Schedule of Events (SoE)

Table 1 Schedule of Events

	Screening	Study Baseline	Treatment Period TP1					TP2 Baseline	Treatment Period TP2					DC [6]		EOS/ FU [7]
Treatment Day (visit window [days])	Day -28 to -2[1]	Day -1	Day 2 (±1)	Day 6 (-2)	Day 13 (-2)	Day 20 (-2)		Day -1 (+5) [1]	Day 2 (±1)	Day 6 (-2)	Day 13 (-2)	Day 20 (-2)		Premature DC		14 Days (+3 days)
Informed consent	X															
Demographics, Medical History, RCC History	X															
Assess subject eligibility against inclusion/exclusion criteria	X	X						X								
Subject Medication and Symptom Log – Dispense, Review, Re-dispense	X	X		X	X	X		X		X	X	X		X		
Record/assess AEs, Concomitant Medications, and Therapies	Continuous		☎	Throughout the Study					☎	Continuous Throughout the Study						
Vital signs including pulse oximetry and weight [2]	X	X		X	X	X		X		X	X	X		X		X
Height, BMI	X															
Electrocardiogram (ECG) - triplicate, central over-read [2]	X	X				X		X				X		X		
Spirometry	X															
Chest Radiograph or Computed Tomography (CT) [4]	X															
Physical examination	X			X	X	X				X	X	X		X		
Clinical laboratory tests [3]	X	X				X		X				X		X		
Pharmacokinetics (PK) blood Sample [3]		X		X	X	X		X		X	X	X		X		
Serum pregnancy test, and contraceptive counselling, if applicable	X	X						X								
Urine pregnancy test (confirm result before dispensing IP), if applicable		X						X								
24 hr Cough monitor - Hook up, remove at home and return after 24-hrs [5]	X	X		X	X	X		X		X	X	X				
e-diary – Dispense and train on use	X															
e-diary – Review e-diary compliance and retrain as necessary		X	☎	X	X	X		X	☎	X	X	X				
e-diary – PRO questionnaires, including sows	As described in the PRO Schedule of Events															
Clinical Global Impression of Severity (CGI-S)		X				X		X				X		X		
Clinical Global Impression of Change (CGI-C)						X						X		X		
Randomization		X														
IP - Dispense blister card, review dosing instructions		X		X	X			X		X	X					
IP - Review compliance			☎	X	X	X			☎	X	X	X				
IP - Review Tolerance and manage symptoms as needed			☎	X	X	X			☎	X	X	X				
Review IP Blister Card and redispense, or retrieve at DC [8]				X	X	X				X	X	X		X		
Retrieve e-diary, Review and retrieve IP and symptom log																X

21 Day Washout Period

AE - Adverse Event DC - Discontinuation EOS - End of Study SOWS - Subjective Opiate Withdrawal Scale IP - Investigational Product PRO - Patient Reported Outcomes TP - Treatment Period FU - Follow-Up
☎ *Telephone Contact*

RIVER Schedule of Events (SoE) Footnotes

1 Screening should be completed within 14 days, with possibility to extend to 28 days without re-screen, for scheduling or logistical reasons. Contact medical monitor regarding extensions beyond the 28 day screening period.
Washout period is 21 days, with a visit window of +5 days. Please contact medical montitor regarding extensions in the washout beyond the +5 day window.

2 Vital signs after at least 5 minutes in sitting position, Triplicate ECG after at least 5 minutes in supine position. Vital signs and ECG to be performed before invasive procedures.
ECG to be transmitted for central over-read, and screening central over-read reports (received within 72 hours) are used to assess eligibility.

3 PK sample to be drawn as soon as possible after the ECG. Labs will be drawn for clinical chemistry, hematology, urinalysis, and coagulation and sent to the central lab.

4 Chest Radiograph or CT: If the assessment has been performed within the last 24 months, a copy of the radiologist report is to be filed in the source as documentation of eligibility.
If not assessed in the last 24 months, or a report is not able to be obtained for review, then the procedure will be performed at screening.

5 Digital cough monitor
- Day of the Visit - hook up for 24-hour recording; monitor will be worn until the following day to obtain at least a full 24-hour recording period of cough frequency.
- After 24 hours - removal and return - At the end of the recording session, the monitor will be removed at home by the subject. Subject to be provided with appropriate shipping material to return monitor after removal, for upload of data to Vitalograph portal. **First dose of IP is taken after the removal of the cough monitor on Day 1.**

6 In case of premature discontinuation of IP, the IRT/e-diary system to be updated immediately to activate the PROs (do not wait for the subject to come to site)
The site should complete discontinuation procedures per the DC Visit Schedule at the current visit OR subject to return to the site for the premature DC visit as soon as possible, if discontinuation occurs between scheduled visits.

7 End of Study/ Safety Follow-up visit will occur 14+3 days after the last dose of IP (last dose can be TP2: Day 20, or earlier in case of premature discontinuation).

8 IP Blister card is to be returned to site by courier together with the cough monitor after removal at Day 21. At Discontinuation visit (if applicable), retrieve blister card.

Table 2 Schedule of Events (SoE) for PROs

	Screening	Baseline [1]	Treatment Period [2]			DC	EOS/FU
Day/Week:	Day -28 to -2	Day -1	Day 7	Day 14	Day 21	DC [5]	FU
CS-VAS	X	X	H	H	H	H	X
LCQ		X			H	H	
Patient-Reported Cough Frequency (PR-CF)	X	Daily from Day -7, and thoughout the study				H	X
PGI-S, Cough		X	H	H	H	H	
PGI-C, Cough			H	H	H	H	
SOWS Baseline [3]		X	H				
SOWS for 14 days after last dose [4]					H	H	

For full PRO titles, refer to the protocol *FU - Follow-Up* *DC - Premature Study Discontinuation*

H PROs completed in the eDiary at home, on the appropriate day as presented in the e-diary.

X PROs completed in the eDiary at the study site .

1 At Baseline, all PROs will be completed during the visit, on the day of cough monitor application.

2 At post baseline visits with a cough monitor, PROS will be completed the day after the per protocol visit date, regardless of when the actual visit is performed.

3 SOWS baseline: will be completed once at Baseline and Day 7 to determine baseline status for relevant symptoms.

4 SOWS: From the last day the subject took IP, regardless of when this occurs, SOWS will be completed daily via e-diary until 14 days after last IP dose. Site will monitor SOWS compliance to confirm subject is completing entries as required.

5 In case of premature discontinuation of IP - PROs to be activated immediately via the IRT/e-diary portal (do not wait for the subject to come to site).

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
AE	adverse event
AR	Autoregressive
ATC	Anatomical and Therapeutic Class
ATS/ERS	American Thoracic Society / European Respiratory Society
BID	twice daily
BMI	body mass index
bpm	beats per minute
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CS-VAS	Cough Severity Visual Analog Scale
CT	Computed Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CV	coefficient of variation
DCF	Data Clarification Form
dl	deciliter
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
EOS	End of Study
ESR	Expedited Safety Report
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FU	Follow-up
FVC	Forced Vital Capacity
g	gram
GCP	Good Clinical Practice
g/dl	grams per deciliter
HCG	human chorionic gonadotropin
HCl	hydrochloride
HT	Hydroxytryptamine
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product (Study Drug)

IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology for IP management
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LCQ©	Leicester Cough Questionnaire
m2	square meter
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mITT	modified intent-to-treat
ml	milliliter
mm	millimeter
ms	millisecond
NA	Not Applicable
NAL ER	Nalbuphine Extended-Release tablets
OTC	over the counter
PBO	Placebo
PD	pharmacodynamics
PGI-C	Patient Global Impression of Change
PID	Patient Identification Number
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
PP	Per Protocol
PR	interval that extends from P wave onset until start of QRS complex
PR-CF	Patient Reported Cough Frequency
PRO	Patient Reported Outcome
QD	once a day
QoL	Quality of Life
QRS	complex representing depolarization of ventricles
QT	interval between the start of the Q wave and the end of the T wave
QTcF	the corrected QT interval by Fridericia
RBBB	Right Bundle Branch Block
RCC	Refractory Chronic Cough
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SNRI	serotonin and norepinephrine reuptake inhibitor
SoE	Schedule of Events
SOP	standard operating procedure
SOWS	Subjective Opiate Withdrawal Scale
SSRI	serotonin reuptake inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCA	tricyclic antidepressant
TdP	Torsade de Pointes

TEAE	Treatment Emergent Adverse Event
TP1	Treatment Period 1
TP2	Treatment Period 2
UK	United Kingdom
umol/l	micromoles per liter
US	United States
USUBJID	Unique Subject ID
WHO	World Health Organization
WOCBP	women of childbearing potential

2. INTRODUCTION

2.1. Background Information on Refractory Chronic Cough

The European Respiratory Society Task Force Report guidelines on the diagnosis and treatment of chronic cough (*Morice et al 2020*) used the term Refractory Chronic Cough to indicate that the cough is refractory to conventional treatment of cough-associated conditions or traits. The terminology of Refractory Chronic Cough (RCC) is a cough that persists despite optimal treatment for the presumed associated clinical condition or in cases where no cough-associated condition is found despite adequate investigation, according to published best practice guidelines in an adherent patient (*McGarvery et al, 2019*).

Chronic cough accounts for 10-38% of patients attending specialist cough clinics in the United Kingdom (UK) and the United States (US), and most commonly occurs in the fifth through seventh decade of life (*Gibson and Vertigan, 2015*). Females compose 66% of the patient population and the median duration of chronic cough was 6.5 years. Referrals of patients with persistently troublesome chronic cough have been shown to account for up to 38% of a US pulmonologist's outpatient practice (French et al 1998).

It is reported that 50% of women in cough clinic report incontinence related to coughing and 80% of patients stated interference with lifestyle and leisure was the commonest complaint in relation to coughing (Young and Smith, 2010).

2.2. Background Information on Nalbuphine

The Sponsor is developing 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 US as Nubain®, on which the presently sold generic injectable formulations are based. Approved indications in the US include the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, as a supplement to balanced anesthesia, pre-operative and post-operative analgesia, and obstetrical analgesia during labor and delivery (*Nubain US Prescribing Information, 2023*). Nalbuphine remains an unscheduled drug in the US (*US Drug Enforcement Agency, Jan 2023; US Dept of Justice List of Scheduling for Controlled Substances, 2023*).

Commercial availability in the European Union (EU) of the parenteral formulation of nalbuphine dates to 1986 (*Medicines Evaluation Board in the Netherlands, 2010*) when the originator product, Nubain 10 mg/ml solution for injection, was registered in the Netherlands by Bristol-Myers Squibb. In 2020, an application from Altamedics GmbH for Nubain 10 mg/ml Injektionslösung was approved in Germany, Austria, and the Netherlands for the for short-term relief of moderate to severe pain and for pre- and post-operative analgesia (*Nubain Public Assessment Report, 2020*). 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, 2022*).

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)*. In addition to a prior phase 2 study in IPF related cough (Clinical Study TR12), the clinical development program of NAL ER tablets has included investigational studies for the treatment of prurigo nodularis related pruritus, uremic pruritus in hemodialysis patients as well as safety and efficacy analgesic studies. Additional information can be found in the Investigator's Brochure (IB).

2.3. Rationale for Investigation of Nalbuphine in Refractory Chronic Cough

There is medical literature reporting that the opioid drug class may be effective antitussives. In chronic cough subjects, morphine may be effective treatment (*Morice et al, 2007; Morice et al, 2020*). Nalbuphine has been shown in human studies to have preventative antitussive effect on acute cough during anesthesia induction (*Wang et al, 2020).* Other mixed agonist-antagonist pharmacologic class of drugs have also been shown to be effective in managing the adverse effect of 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 (*Torbutrol® US Package Insert, 2013*).

Integration of cough reflex behavior that occurs at brainstem level (*Canning et al, 2014*) may be modulated by nalbuphine pharmacologic action given the high density of opiate receptors (*Volkow and McLellan, 2016*) Opiate receptors in the cerebrum may also potentially be modulated by nalbuphine pharmacologic action where cortical mediated control of cough is an important regulator of the cough reflex set point (*Mazzone et al, 2009*).

Since opiate receptors are also located at the peripheral nerve level (*Volkow and McLellan, 2016*), this is an additional potential site of pharmacologic action of nalbuphine that may be important given the "cough hypersensitivity syndrome" hypothesis that inflammation-induced effects ("neuro-inflammation") in the neural pathways between the airway tissue and the brain may lead to refractory cough (*Morice et al, 2014*; *McGarvey and Gibson, 2019*).

2.4. Rationale for Study Design and Control Group

The purpose of the NAL04-201 study is to evaluate the safety and efficacy of NAL ER titrated to 108 mg BID compared to placebo (PBO) in RCC patients.

The primary study endpoint, change in 24-hour 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 who summarized the CHEST Expert Panel recommendations regarding tools to be used in clinical trials assessing cough (*Boulet et al, 2015*). The Panel recommended that acoustic cough counting to assess cough frequency should be done through objective means. Secondary endpoints include PRO measures that have been studied in RCC programs.

The TR12 study in chronic cough in IPF successfully utilized the same study design planned for the NAL04-201 study. TR12 was a randomized, double-blind, placebo (controlled, crossover trial with two 22-day treatment periods (1: NAL ER-PBO; 2: PBO-NAL ER) separated by a 2-week washout using an objective digital monitor (VitaloJAK®). Subjects treated with doses escalating to 162mg BID of NAL ER showed a 76.1% improvement (95% CI, −83.1 to −69.1) in the geometric mean percent change in objective cough frequency compared with 25.3% (95% CI, −43.9 to −6.7) in placebo-treated subjects, with a 50.8% placebo-adjusted change (P<0.0001).

The purpose of this present study is to evaluate the safety and efficacy of NAL ER titrated to 108 mg BID compared to placebo in RCC patients.

Centrally active drugs are typically titrated in order to minimize the incidence and severity of AEs that can occur with drug initiation; thus, NAL ER is titrated to the target dose of the respective randomized study arm (see *Table 3 Dosing Scheme*). The AEs most commonly associated with titration involve the central nervous system (CNS) (nausea, headache and dizziness) and gastrointestinal (nausea and vomiting) organ systems (see *Section 8.21 Tolerance and Titration Symptoms Management*). A similar titration rate of NAL ER has been safely used in the IPF TR12 study and in other study populations (see IB for details) and the titration rate is consistent with opioid class guidelines such as the "three-day tolerance check" (*National Opioid Use Guideline Group Canada, 2010*) and "five ½ life" rule (*CDC Guideline for Prescribing Opioids for Chronic Pain, 2016*). In the TR12 trial subjects were escalated from 27 mg QD to 54 mg, to 108 mg and then 162 mg BID dose levels on Days 5, 9 and 16. In the present study, subjects will be escalated from 27 mg QD to 54 mg BID and then to 108 mg BID on Days 7 and 14.

The study staff, subjects, and Sponsor/clinical research organization (CRO) clinical staff will all be blinded to treatment assignment/sequence to avoid potential bias. This study will be conducted in compliance with the protocol and with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

The use of placebo as a comparator is justified for this study due to:

- The study assessing NAL ER in addition to treatments for underlying conditions (participants should continue their therapies for underlying etiologies)
- The negative consequences of not receiving treatment are low (not a life-threatening disease)
- Need to maintain the study blinding, allowing for an unbiased assessment of efficacy and safety.

2.5. Risk/Benefit and Ethical Assessment

Nalbuphine is currently in medical use as a parenteral formulation (*Nalpain UK package insert, 2011; Nubain US Prescribing Informationt, 2023*) indicated for analgesia management as well as in the US as a supplement to anesthesia. The highest dose proposed in the current clinical study is 108 mg BID (216 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 Subjective Opiate Withdrawal Scale (SOWS) reporting has been incorporated into the study.

The TR12 study in patients with IPF-associated chronic cough demonstrated that subjects treated with doses escalating to 162 mg BID of NAL ER showed a 76.1% improvement (95% CI, −83.1 to −69.1) in the geometric mean percent change in objective cough frequency compared with 25.3% (95% CI, −43.9 to −6.7) in placebo-treated subjects, with a 50.8%

placebo-adjusted change (P<0.0001). In TR12, cough PRO measurements, including daily EXACT2 Cough Frequency Scores and the CS-NRS measure of cough severity, revealed large cough effect size reductions at end of treatment, with near maximal effects on cough PROs seen at Day 8/9 when subjects were taking the 54 mg BID dose of NAL ER. The 108 mg BID dose of NAL ER in TR12 produced similar effects on cough PROs to those of the 162 mg BID dose level, so the maximal dose in the current RIVER study is 108 mg BID.

The prescribing information for parenterally administered nalbuphine states that the drug may produce the same degree of respiratory depression as an equianalgesic dose of morphine; it also states that the drug exhibits a ceiling effect such that increases in dose greater than 30 mg nalbuphine HCl salt (27 mg free base) do not produce further respiratory depression in the absence of other CNS active medications affecting respiration. (*Nubain US Prescribing Information, 2023)*. Route of administration is also likely to affect the risk for respiratory depression. Based on the safety data obtained to date in the study populations investigated with oral NAL ER, no safety signals related to respiratory function impairment have been identified. This includes the TR12 study in idiopathic pulmonary fibrosis (IPF) patients studied with doses of up to 162 mg BID of NAL ER, compared to the maximal dose of 108 mg BID of NAL ER planned for this study.

Because of the rare but potentially life-threatening condition of serotonin syndrome that can result from the concomitant administration of serotonergic drugs, subjects should be on a stable dose of any medications that may induce serotonin syndrome during the study. Subjects will be informed of the symptoms of serotonin syndrome of which to be aware.

Because NAL ER is metabolized through the cytochrome (CYP) pathway, use of strong inhibitors or inducers of the P450 isozymes is prohibited unless subjects are on a stable dose before and during the course of the study.

In summary, there is evidence for potential benefit of NAL ER treatment in RCC, including improvement in objective cough frequency and patient reported outcomes for patients with chronic cough, based on results of a recently completed Phase 2a study of NAL ER in IPF-associated cough (TR12). The risk for subjects participating in this current study is judged to be low based on previous experience with oral administration of NAL ER, including the TR12 study in IPF patients studied with doses of up to 162 mg BID of NAL ER. The current study in RCC patients will utilize a low initiation dose of 27 mg QD and a gradual dose titration schedule up to a maximal dose of 108 mg BID. Careful safety monitoring of subjects will be performed during the clinical study. Investigators will be educated regarding the symptoms of rare but significant AEs that are linked to the opiate class.

3. STUDY OBJECTIVES

3.1. Primary Objective:

Objective	Endpoint
Effect of treatment on 24-hour cough frequency (coughs per hour) after 21 days	• Relative change from Baseline in 24-hour cough frequency (coughs per hour) as assessed by objective cough monitoring at Day 21 for NAL ER compared with placebo.

3.2. Secondary Objectives:

Objective	Endpoint
Safety and tolerability of NAL-ER for the treatment of Refractory Chronic Cough (RCC)	• Adverse events, clinical laboratory assessments, vital signs, and physical examination summaries. • ECG summaries [ECGs will be analyzed in a separate report]. • Subjective Opiate Withdrawal Scale (SOWS) daily summaries for the 14 days following the last dose of investigational product.
24-hour cough frequency (Coughs per hour)	• Relative change from Baseline in 24-hour cough frequency (coughs per hour) at Days 7 and 14 for NAL ER compared with placebo. • Proportion of responders with ≥30%, ≥50% and ≥75% reduction in the 24-hour cough frequency at Days 7, 14, and 21 for NAL ER compared with placebo.
Awake cough frequency (Coughs per hour)	• Relative change from Baseline in awake cough frequency (coughs per hour) at Days 7, 14, and 21 for NAL ER compared with placebo.
Sleep cough frequency (Coughs per hour)	• Relative change from Baseline in sleep cough frequency (coughs per hour) at Days 7, 14, and 21 for NAL ER compared with placebo.
CS-VAS (Cough Severity Visual Analogue Scale)	• Change from Baseline in the Cough Severity Visual Analogue Scale at Days 7, 14, and 21 for NAL ER compared with placebo.
LCQ© (Leicester Cough Questionnaire)	• Change from Baseline in the LCQ total score at Day 21 for NAL ER compared with placebo.
Patient-Reported Cough Frequency (PR-CF)	• Change from Baseline in the PR-CF at Days 7, 14, and 21, for NAL ER compared with placebo. • Proportion of PR-CF responders, with response defined as at least a one category improvement at Days 7, 14, and 21 for NAL ER compared with placebo.

PGI-S, PGI-C, Cough (Patient Global Impression of Severity and Change for Cough)	• Change from Baseline in the PGI-S Cough at Days 7, 14, and 21 for NAL ER compared with placebo. • PGI-C Cough score at Days 7, 14, and 21 for NAL ER compared with placebo.
CGI-S, CGI-C, Cough (Clinical Global Impression of Severity and Change for Cough)	• Change from Baseline in the CGI-S Cough at Day 21 for NAL ER compared with placebo. • CGI-C Cough score at Day 21 for NAL ER compared with placebo.

Pharmacokinetics: Nalbuphine (and/or metabolites) plasma concentration will be measured for each treatment group at all visits where subject is on treatment. A PK sample will be drawn and correlated with the time of IP intake as reported by the subject.

4. INVESTIGATIONAL PLAN

4.1. Study Duration and Dates

The planned study period is from

- Estimated **first subject randomized in Q3 2023**, until
- Estimated **last subject completed in 2024.**

which includes an approximately 12-month recruitment period, and 3-month study period, including screening and safety follow-up (FU)/end of study (EOS). The overall end of study is defined as the last study visit for the last patient (LPLV).

The duration of participation for each subject will be up to 15 weeks and includes the following:

- **Screening Period**: Day -28 to Day -2. Screening should be completed within 14 days, with the possibility to extend to 28 days without re-screen for scheduling or logistical reasons.
- **Treatment Period 1**: 21 Days (-2 days visit window at each visit)
- **Washout**: 21 Days (+5 days)
- **Treatment Period 2**: 21 Days (-2 days visit window at each visit)
- **Safety Follow-up**: 14 (+3 days) days after the last study treatment administration.

Actual overall study duration and/or recruitment period may vary. Following their participation in the study, subjects will return to the care of their usual physician for the continued management of their condition or, if needed, they will be referred to appropriate care.

4.2. Overall Study Design and Plan

A double-blind, randomized, placebo-controlled, 2-period crossover study for the treatment of cough in subjects with Refractory Chronic Cough.

Based on the screening cough monitor results, the study will enroll subjects in a 1:1 ratio to subgroups of 10-19 coughs/hour and ≥20 coughs/hour.

After meeting eligibility during the screening period, subjects will be randomly assigned (1:1) to one of the following sequences:

- NAL ER in Treatment Period 1, followed by PBO in Treatment Period 2

  OR

- PBO in Treatment Period 1, followed by NAL ER in Treatment Period 2

The 21-day treatment periods are separated by a 21-day washout period. NAL ER will be titrated according to the *Table 3 Dosing Scheme*.

Study visits in each treatment period will be at Day -1 for Baseline cough assessments, and at Days 6, 13, and 20. Visits and Assessments are described in *Figure 1 Study Schematic*, and *Section 1.2 Schedule of Events, Table 1 and Table 2*. Subjects will have blood drawn for pharmacokinetic (PK) analysis of nalbuphine plasma concentration. Subjects will also

complete questionnaires for efficacy evaluations and undergo safety evaluations including an electrocardiogram (ECG).

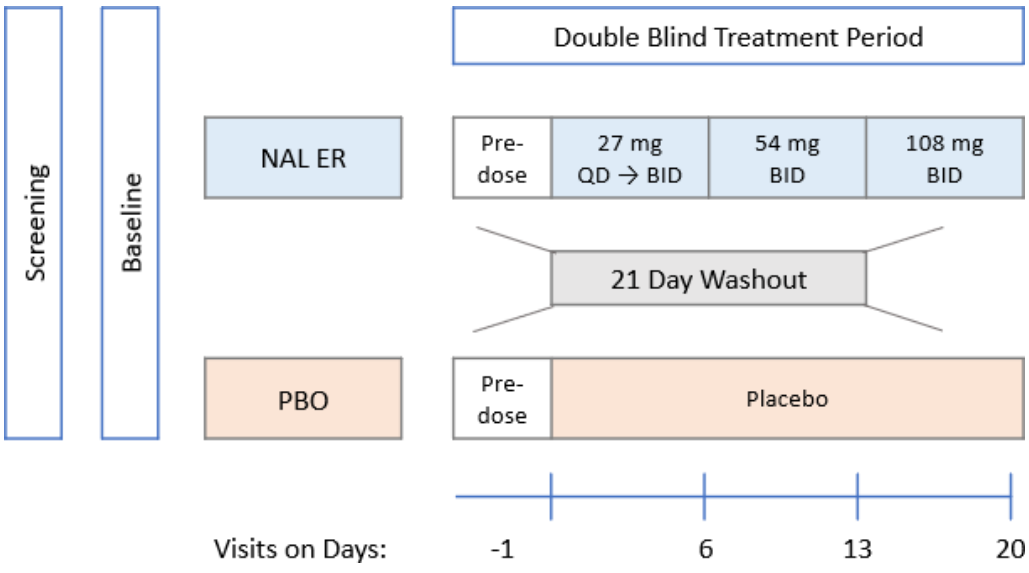
At the Screening and Baseline visits and on Days 6, 13, and 20 during each treatment period, site staff will place an electronic cough monitor on the subject, which will be worn for a 24-hour recording period to assess cough frequency. At the end of each recording session (Days 7, 14, and 21), the monitor will be removed at home by the subject, and the subjects will complete Patient Reported Outcomes (PROs) questionnaires in the diary. The monitor will be returned to the clinical study center for processing.

Subjects will be taken off study drug at the end of the Treatment Period 2 and followed off treatment for an additional 2 weeks.

If permanent discontinuation of investigational product occurs, the discontinuation and safety follow-up/EOS visits should be performed. End of Study for any participant will occur when the safety follow-up visit is completed,14+3 days after last dose, or withdrawal of consent.

4.2.1. Study Schematic

Figure 1 Study Schematic



5. STUDY POPULATION SELECTION

5.1. Study Population and Sites

Approximately 60 subjects with diagnosed Refractory Chronic Cough will be randomized, across approximately 12-16 centers.

Subjects will be enrolled in a 1:1 ratio to subgroups of 10-19 coughs/hour and ≥20 coughs/hour.

5.2. Inclusion Criteria

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

1. Current **diagnosis of refractory chronic cough** (RCC), and history of cough for at least one year.
   Defined in the ERS Guidelines as chronic cough that is refractory to conventional treatment of cough-associated conditions or where no cough-associated conditions can be identified (*Morice et al, 2020*).
2. **Chest radiograph or computed tomography (CT)** of the thorax performed within the last 24 months and after the onset of chronic cough or during the screening period not demonstrating any abnormality considered to be significantly contributing to the refractory chronic cough in the opinion of the Principal Investigator.
3. Score of **≥40mm on the Cough Severity VAS** at the Screening visit.
4. 24-hour objective **cough frequency ≥10 or ≥20 coughs/hour** based on cough monitor recording performed during the Screening Period, with results reviewed prior to baseline visit. Study will enroll subjects in a 1:1 ratio to subgroups of 10-19 coughs/hour and ≥20 coughs/hour.
5. **FEV1 / FVC ratio ≥ 60%** as determined by spirometry adhering to ATS/ERS guidelines. (*Graham et al, 2019*).
6. Males or females ages 18 years and older at the time of consent.
7. Willing and able to provide written informed consent, comply with study requirements and restrictions, and agree to the confidential use and storage of all data and use of all anonymized data for publication including scientific publication.

5.3. Exclusion Criteria

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

1. Clinical diagnosis of **sleep apnea** and/or use of CPAP.
2. Upper or lower **respiratory tract infection** or change in pulmonary status in the last 6 weeks prior to the baseline visit.
3. History of **bronchiectasis, chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF)** or other significant respiratory disorder that might effect cough.
4. History of **uncontrolled asthma**.

5. Current **smokers/vapers**, individuals who have given up smoking ≤12 months, individuals using nicotine patches, gum, or any other nicotine supplements, or individuals with a smoking history of 20 pack-years or more.
6. **Speech therapy/physiotherapy for RCC** is acceptable if the subject has started the therapy at least 4 weeks prior to the Baseline visit and continues the therapy through the Treatment Periods. It may not be started within 4 weeks of starting the study or for the duration of the study.
7. **Cardiac Safety:** Mean QTcF value of 3 centrally read screening Electrocardiograms (ECG) calculated as
   a) ≥470ms if QRS <120ms or
   b) ≥500ms in the presence of either a Right Bundle Branch Block (RBBB) or QRS≥120ms
8. **Heart Rate** <50 bpm or >100 bpm, as determined by vital signs pulse obtained over 30-60 seconds
   a) Subjects with a resting heart rate of <50 bpm will have it repeated once after 5 minutes in the supine position, and if it remains <50 bpm during the repeat, they will be considered a screen failure.
   b) Subjects with a rate >100 bpm should be considered a screen failure. Rescreening may be possible with the approval of the medical monitor, after medical or alternative management of the atrial fibrillation.
9. **Kidney Function**: Estimated glomerular filtration rate ≤ 44 mL/min/1.73 m^2 at Screening.
10. **Liver Function**: Total Bilirubin >3mg/dl [>50umol/L] and Serum Albumin <2.8g/dl
11. History of 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.
12. History of **substance abuse** including excessive alcohol consumption, that in the opinion of the Investigator, may interfere with the conduct of the study.

    Alcohol consumption should be limited for the duration of study treatment.
13. **Significant medical condition** or other factors as assessed by the investigator that may interfere with the subject's ability to successfully complete the study.
14. **Pregnant or lactating female subject**. Women of childbearing potential (WOCBP) must use an acceptable method of birth control and have a negative pregnancy test at the screening and baseline visits. WOCBP and acceptable methods of birth control are defined in the protocol,

    Section 8.13 WOCBP Pregnancy test, and contraceptive counselling.
15. Known **intolerance** (gastrointestinal, central nervous system symptoms), hypersensitivity, drug allergy following the use of an opioid drug.
16. Known hypersensitivity to nalbuphine or to NAL ER excipients.
17. Previous enrollment in a NAL ER clinical study.
18. Concurrent enrollment in an **ongoing clinical trial** or anticipated enrollment in a concurrent clinical trial. Observational or long-term safety follow-up studies (e.g., in a vaccine study) may be allowed upon medical monitor approval.

Medication-related Exclusions:

(Refer to protocol *Section 8.6.1 Prohibited and Restricted Medications, and Washout*):

19. Use of **opiates** is prohibited within 14 days prior to the baseline visit. Includes opiate-containing anti-cough agents, and naltrexone. Subjects are prohibited from using opioids for the duration of the study.
20. Use of **benzodiazepines** are prohibited within 14 days prior to the baseline visit and for the duration of the study.
21. **Monoamine oxidase inhibitors** (MAOIs) including methylene blue (methylthioninium chloride) and the antibiotic linezolid are prohibited within 14 days prior to the baseline visit and for the duration of the study.
22. Exposure to any **investigational medication**, including placebo, is prohibited within 4 weeks prior to the baseline visit and for the duration of the study.
23. Use of **pregabalin, gabapentin, baclofen, tricyclics, or thalidomide** given for the treatment of cough is prohibited within 14 days of the Baseline visit, and for the duration of the study.

    Pregabalin, gabapentin, baclofen, tricyclics, or thalidomide required for other indications, is permitted if on a stable dose for at least 4 weeks, and still experiencing significant cough, and expected to remain on that dose for the duration of the study.
24. Use of **ACE inhibitors** is prohibited within 12 weeks prior to the baseline visit, and for the duration of the study (due to potential for causing cough).
25. Other medications prescribed as **cough suppressants** (such as dextromethorphan or benzonotate) are prohibited unless on a stable dose 14-days prior to the baseline visit and are expected to remain on that dose for the duration of the study.
26. Medications prescribed for **asthma, rhinitis/upper airway cough syndrome, or gastroesophageal reflux** disease are prohibited unless on a stable dose for 14-days prior to the baseline visit and are expected to remain at that dose for the duration of the study.
27. Use of **medications that affect serotonergic neurotransmission a**nd that when used concomitantly with opioids can cause serotonin syndrome are prohibited unless on a stable dose for 14-days prior to the baseline visit and are expected to remain on that dose for the duration of the study.
28. **Strong inhibitors/inducers of the P450 Isozymes** are prohibited unless on a stable dose for 14-days prior to baseline visit and are expected to remain on that dose for the duration of the study.
29. Use of a medication having a "known risk" of Torsade de Pointes (TdP) (categorized as "KR" on the *Credible Meds® website*) is prohibited at entry or during the study. Medications associated with a potential risk of QT prolongation, but not clearly associated with TdP, 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 baseline.
    - 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.

6. STUDY TREATMENT

6.1. Description of Treatment(s)

6.1.1. Study Drug

The investigational product (IP) in this trial is nalbuphine ER tablets (NAL ER). The NAL ER tablets are round, white to off-white, film-coated tablets containing either 27 or 54 mg of nalbuphine (equivalent to 30 or 60 mg nalbuphine HCl); the 27 or 54 mg NAL ER round tablets are identical in appearance. The NAL ER tablets will be provided by the Sponsor.

6.1.2. Placebo

The matching placebo tablet supplied is identical in appearance to the 27 and 54 mg tablets respectively and will be packaged identically to the IP.

6.2. Treatments Administered

Administration of the investigational product will be according to the dosing scheme in *Table 3 Dosing Scheme*. Dosing will consist of 2 tablets for the AM dose and 2 tablets for the PM dose.

For subjects assigned to one of the NAL ER arms, the dose will be titrated from a starting dose of 27 mg QD to 108 mg BID over the treatment period.

6.2.1. Dosing Scheme

Table 3. Dosing Scheme

Grey shading indicates cough monitor application and recording period.

VISIT	Study Day (TP1 or TP2)	NAL ER Dose (mg)		PLACEBO (PBO)	
		AM	PM	AM	PM
Baseline	-1	—	—	—	—
	1	—	27	—	PBO
	2	—	27	—	PBO
	3	27	27	PBO	PBO
	4	27	27	PBO	PBO
	5	27	27	PBO	PBO
Day 6	6	27	27	PBO	PBO
	7	27	54	PBO	PBO
	8	54	54	PBO	PBO
	9	54	54	PBO	PBO
	10	54	54	PBO	PBO
	11	54	54	PBO	PBO
	12	54	54	PBO	PBO
Day 13	13	54	54	PBO	PBO
	14	54	108	PBO	PBO
	15	108	108	PBO	PBO
	16	108	108	PBO	PBO
	17	108	108	PBO	PBO
	18	108	108	PBO	PBO
	19	108	108	PBO	PBO
Day 20	20	108	108	PBO	PBO
	21	108	—	PBO	—

6.3. Dispensing and Intake Instructions

The blinded IP kit number will be dispensed using the Interactive Response Technology (IRT) system, and the corresponding kit will be dispensed to the subject. The Study staff will review the dosing instructions with the subject, including counselling on the options for management of possible symptoms during titration.

Investigational product is taken orally and must be swallowed whole without crushing or chewing. Subjects will be instructed to take the investigational product tablets twice per day (BID) with a glass of water, and preferably with food.

If a dose is missed and there are less than 8 hours until the next planned dose, the subject should skip the dose.

Subjects will be informed 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, and to limit alcohol consumption for the duration of study treatment.

6.4. Subject Compliance and Accountability

Subject Compliance and Accountability are assessed through the drug accountability records. Subjects will be instructed to retain the blister cards and return them at the next visit, even if they are partially or completely empty.

Accountability will be determined through an accurate and current documentation of the IP dispensed and returned for each subject, recorded on the appropriate investigational product accountability forms and in the IRT system by a member of the study site staff.

Compliance is defined as the amount of investigational product that should have been taken by a subject based on the dosing instructions provided during a period, compared to what they actually took, based on the number of tablets returned. This is typically expressed as percent (%) compliance.

Compliance will be monitored:

- after each investigational product return, based on the information on the investigational product accountability forms,
- between visits, via subject contact - if the subject is not able to take their medication as scheduled at any time, they should contact the site, and site should support them in maintaining full compliance where possible.
- Plasma samples taken for PK will be blinded during the study, and nalbuphine plasma concentrations will verify compliance for the purposes of analysis.

Dosing and/or compliance discrepancies (above or below 100%), will be noted in the eCRF for the applicable subject visit.

For compliance over 100% and the definition of overdose, refer to *Section 7.5 Overdose*.

6.5. Multiple Missed Doses

If the subject misses 3 or more consecutive doses (equivalent to approximately 1.5 days), contact the study Medical Monitor to discuss the situation and, if needed, dosing instructions (See also *Section 8.21 Tolerance and Titration Symptoms Management and Section 8.22 Premature Discontinuation / Removal of Subjects from the Trial or Study Drug*). 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.

6.6. Randomization and Blinding

Randomization will be performed, and blinding maintained, via IRT. 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 the NAL ER-PBO or PBO-NAL ER arm. The study will enroll subjects in an approximate 1:1 ratio based on objective cough/hour to a 10-19 cough/hour subgroup and a ≥20 coughs/hour subgroup. As recruitment is predicted to be quicker for the 10-19 cough/hour subgroup when the 10-19 cough/hour subgroup has reached its target of approximately 30 subjects randomized, recruitment will be stopped for that subgroup.

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 IRT.

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

Randomization will be stratified by baseline 24-hour cough frequency (10-19 cough/hour vs >20 cough/hour) and sex.

6.7. Investigational Product Supplies Management

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

6.7.1. Packaging and Labeling

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

6.7.2. IP Storage

Store NAL ER tablets and placebo tablets below 25°C (77°F), do not refrigerate, and do not freeze. The investigational product should be stored away from any extreme conditions of temperature, light, or humidity as an additional precaution.

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.

6.7.3. Accountability

The Investigator must maintain accurate records in the study documents and IRT system, of the receipt, dispensation and return of all investigational product shipped by the Sponsor or the Sponsor's representative, including but not limited to date, lot number, expiration date, and amount.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Subjects will be closely monitored for safety throughout the study. In addition to adverse events, vital signs including pulse oximetry, ECGs reviewed by the Investigator, physical examinations, and clinical laboratory testing will be conducted to monitor subject safety. To monitor for possible withdrawal symptoms, subjects will complete the SOWS daily for 14 days following each treatment period. Details of assessments are provided in *Section 8 Study Activities and* Procedures.

7.1. 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 and which does not necessarily have a causal relationship with treatment. The Investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

The AE may be any of the following:

- 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
- 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 two 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 but rather 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.

7.2. Reporting of Adverse Events

All AEs occurring during the study will be collected on the AE eCRF.

Clinically relevant findings on ECG, laboratory testing, or physical examination during Screening (i.e., after the signing of the informed consent form and prior to the first dose of IP) should be recorded on the Medical History eCRF unless considered to be acute or caused by a study procedure in which case they are to be recorded on the Adverse Event eCRF.

All serious adverse events and non-serious adverse events other than those described above with an onset during Screening should be recorded on the Adverse Event eCRF. All Adverse Events with onset after exposure to any amount of study drug are to be recorded on the Adverse Event eCRF.

Starting from the point when the subject signs the Informed Consent Form (ICF), 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.

During visits, phone calls, or other study contacts, study staff will solicit information using open ended questions, and document volunteered information regarding adverse events.

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 study.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF.

Laboratory abnormalities will be recorded as adverse events only if they are associated with 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.

7.2.1. Events Exempt from Adverse Event Reporting

As cough is an endpoint in this study, it will NOT be reported as an adverse event. Refer to *Section 8.15 24-Hour Digital Cough Monitor* and *Section 8.16 Patient Reported Outcome (PRO) Questionnaires* for additional details regarding data collection for cough.

7.2.2. Adverse Events Requiring Additional Narratives

As part of the formal investigation of a drug that is classified as CNS active opioid, certain adverse events will be documented in more detail to support an eight-factor analysis. The following AE preferred terms will require an additional narrative in the eCRF:

Table 4 Adverse Events Requiring Additional Narratives

Behavioral addiction	Feeling drunk
Dependence	Hallucinations (any)
Dissociation	Intentional product misuse
Drug abuser	Overdose (see also *Section 7.5 Overdose*)
Drug dependence	Prescription form tampering
Drug detoxification	Product tampering
Drug diversion	Substance abuse
Drug use disorder	Substance dependence
Drug withdrawal convulsions	Substance use disorder
Drug withdrawal syndrome	Withdrawal syndrome
Euphoric mood	

7.2.3. Timing

Adverse events experienced by a subject starting from **signing of informed consent until the last safety follow-up/EOS**, will be recorded in the Adverse Event or Medical History eCRF as appropriate.

Any clinically significant abnormal findings identified during the screening period (e.g., laboratory, physical exam) will be documented in the medical history (see *Section 8.2 Demographics, Medical History, RCC History*).

Any (S)AE still unresolved at the safety follow-up/EOS or 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.

7.2.4. Severity Grading

All AEs will be reported and graded, if possible, using the current version of *Common Terminology Criteria for Adverse Events (CTCAE)*.

The AE terms that are not found in the most current version of CTCAE will be graded according to the general guideline in *Table 5 CTCAE Severity Grading*:

Table 5 CTCAE Severity Grading

Grade	Comment
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

Every effort will be made to obtain an adequate evaluation of the severity of an AE. An AE that is assessed as severe should not be confused with a serious adverse event (SAE). Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in *Section 7.3.1 Serious Adverse Event Definition*.

7.2.5. Relationship to Study Drug

The investigator will assess the relationship of any AE to the study drug (NAL ER or placebo) using the guidelines presented in *Table 6 Adverse Event Relationship to Study Drug*.

Table 6 Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Definitely related	• 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	• 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	• 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	• 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	• 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

7.3. Serious Adverse Events

7.3.1. Serious Adverse Event Definition

A serious adverse event (SAE) is defined by regulation as any AE occurring at any dose that results in any of the following outcomes:

- death,
- life-threatening AE,
- hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity,
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. These should also be considered to be SAEs.

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 lasting for at least 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.

7.3.2. Reporting Serious Adverse Events to the Sponsor

The study site will report any SAE to the Sponsor or their designee, without regard to causality, within 24 hours after becoming aware of its occurrence.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be reported to the Sponsor as a new SAE within 24 hours.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the study drugs. Information not available at the time of the initial report (e.g., an end date for the SAE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant info is available.

All SAEs must be reported via the electronic data capture (EDC) system within 24 hours of Investigator's knowledge of the event. If the EDC is not available, paper reports should be used and the EDC must be updated with the information on the paper report as soon as the EDC is available.

Paper reports must be emailed to the following address within 24 hours:

[redacted]

Follow-up information on SAEs must also be reported by the Investigator within the same time frames.

7.3.3. Regulatory Aspects of SAE Reporting

The Investigator will promptly report all SAEs to the Sponsor or their designee within the timeframe specified in *Section 7.3.2 Reporting Serious Adverse Events to the Sponsor*. Prompt notification of SAEs by the Investigator is essential so that the Sponsor can meet legal obligations and fulfill ethical responsibilities towards the safety of all subjects participating in their sponsored investigational trials.

The Investigator will comply with the applicable local regulatory requirements related to reporting of SAEs to his or her Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

A given SAE may qualify for submission to applicable regulatory authorities (e.g., submission of SUSARs to EudraVigilance in the EU) as an Expedited Safety Report (ESR) if the SAE is both attributable to study drug and unexpected. In this case, all Investigators participating in a NAL ER study will receive a copy of the ESR.

Assessment for expectedness for SAEs will be determined by the Sponsor using reference safety information specified in the current IB or relevant local label, as applicable.

The ESRs are prepared according to the Sponsor's policy and are forwarded to the Investigator, as necessary. The purpose of the ESR is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation. When a study site receives from the Sponsor an Initial or Follow-Up ESR or other safety information (e.g., a revised Investigator's Brochure), the Investigator is required to promptly notify his or her IRB or IEC.

7.4. Pregnancy

Female subjects who become pregnant should be immediately discontinued from study drug if applicable, and she should complete the discontinuation and safety follow-up visits, and be followed to determine the outcome of the pregnancy. Generally, follow-up will be completed no later than 6 to 8 weeks following the estimated delivery date.

Pregnancy itself is not considered an adverse event or SAE, however pregnancy information on female subjects will be collected with the same process as for an SAE (see *Section 7.3 Serious Adverse Events*). Any pregnancy complications or less than a healthy, normal outcome will be recorded as an adverse event or SAE.

7.5. Overdose

Overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question).

In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the Investigator has reason to suspect that the subject has taken the additional dose(s).

Overdose is one of the AEs which require an additional narrative in the eCRF (see *Section 7.2.2 Adverse Events Requiring Additional Narratives*).

In the event of clinical overdose, the effects of nalbuphine may be reversed with opioid antagonists such as naloxone. Such events require urgent medical attention and sustained observation over several hours. Please see the IB for additional information.

8. STUDY ACTIVITIES AND PROCEDURES

The study activities are described in detail in *Section 1.2 Schedule of Events, Table 1 and Table 2*. This table is the definitive source of the schedule for visits and procedures throughout the study.

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

An Informed Consent Form (ICF) will be prepared that includes information about the study for the subject, and documentation of subject informed consent in writing. 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 will be in a language understandable to the subject and will specify who informed the potential subject. Where required by local law, the person who informs the potential subject must be a physician.

The ICF will be given to the subject to read, and the study will be explained by a qualified member of the study staff. 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.

The informed consent form will be performed on paper. A copy or second original of the signed ICF must be given to the subject to keep. One original signed ICF will be retained by the Investigator.

8.2. Demographics, Medical History, RCC History

The subject's demographics and medical history will be documented, including age, sex, body weight, height and body mass index (BMI). Race and/or ethnicity will be collected where possible in accordance with local regulations.

Clinically significant abnormal findings identified during the screening period for the first time but indicative of existing condition (e.g. laboratory, physical exam) will be documented in the medical history.

RCC history will include history of smoking, speech therapy/physiotherapy for RCC, and other cough treatments.

8.3. Assess subject eligibility against inclusion/exclusion criteria

The investigator will assess the eligibility of the subject during the screening period and will confirm their eligibility prior to randomizing. At the point that the subject is found not eligible, further screening procedures are not required, and can be documented as not done. For unique circumstances that may justify rescreening, Investigators may contact the Medical Monitor to discuss and obtain approval for rescreening.

8.4. Subject Medication and Symptom Log

Subject Medication and Symptom Logs will be provided to fill in at home by the subjects in between visits.

- On the Subject Symptom Log any new and/or changed symptoms or side effects that bother the subject will be reported during the study.
  The symptom log will be reviewed by staff and applicable AEs reported and entered in eCRF.
- On Subject Medication Log the addition of new, changes in the dose, or discontinuation of any non-study medications including oxygen therapy, speech therapy/physiotherapy for RCC, over-the-counter (OTC) medications, herbal medications, vitamins, and nutritional supplements will be reported.
  The medication log will be reviewed by staff and applicable information entered in eCRF.

Subjects should be instructed to bring the logs to every visit and have them ready during the check-in phone calls. The logs should be reviewed and re-dispensed, if applicable. The logs are to be retrieved once full or at the end of the study, and filed in the subject file.

8.5. Adverse Event Assessments

Refer to *Section 7 Adverse Events and Serious Adverse Events* for full details on safety management and recording of adverse events.

8.6. Concomitant Medication and Therapy Assessments

Subjects may receive all clinically indicated medications and therapies during the study with the exceptions noted in *Table 7*.

Any medication or therapy including oxygen therapy, speech therapy/physiotherapy for RCC, over-the-counter (OTC) medications, herbal medications, vitamins, and nutritional supplements taken and their reason for use will be recorded in the Concomitant Medication eCRF from **14 days prior to the first day of the screening** until the last safety follow-up.

Each subject will be instructed to report the use of all new and/or changed medications on the study specific medication log, and to bring the log to each study visit for review (See *Section 8.4 Subject Medication and Symptom Log*). Subjects will also be instructed about the importance of not taking any new medications during the study (including OTC medications) without consulting the Investigator.

If the subject begins taking or requires changes to dosage regimen of a prohibited or restricted medication after screening, it will be determined if the subject may continue in the study upon consultation with the sponsor. Such medications or dosage changes are to be collected and recorded in the Concomitant Medication eCRF.

Concomitant procedures and surgeries, will be collected in the Procedures and Surgeries eCRF.

8.6.1. Prohibited and Restricted Medications, and Washout

The medications described in *Table 7* are prohibited or restricted during the study: If clinically necessary changes to medications that should be stable, or a prohibited medication is taken, the subject does not need to be automatically withdrawn from the study, unless there is a safety

issue (e.g. MAOIs, Benzodiazepines, and sedative hypnotics). The Investigator should continue the subject in the study and contact the medical monitor for instructions.

For the purposes of this table, stable dose is defined as maintenance of a similar dose, frequency, and formulation for a particular drug for the specified period, including as needed dosing (PRN).

Table 7 Prohibited and Restricted Medications, and Washout Period

Medication	Restriction	Washout Period
Opioid Medications, including opiate containing cough suppressants	Prohibited throughout the study	14 days prior to the baseline visit
Opioid antagonists (e.g., naloxone, naltrexone)	Prohibited throughout the study unless required for urgent reversal of opioid adverse effects or clinical opioid overdose	14 days prior to the baseline visit
Benzodiazepines and sedative hypnotics	Prohibited throughout the study	14 days prior to the baseline visit
Monoamine oxidase inhibitors (MAOIs)	Prohibited throughout the study	14 days prior to the baseline visit
Any other investigational Product, including placebo	Prohibited throughout the study	4 weeks prior to the baseline visit
Pregabalin, gabapentin, baclofen, tricyclics, or thalidomide	Prohibited throughout the study for cough indications. OR Stable Dose throughout the study for other (non-cough) indications	For cough: 14 days prior to the baseline visit For non-cough Stable dose for at least 4 weeks, and still meet cough inclusion criteria
ACE inhibitors	Prohibited throughout the study	12 weeks prior to the baseline visit
Use of a medication having a "known risk" of TdP (categorized as "KR" on the *Credible Meds® website*.)	Prohibited throughout the study	4 weeks prior to the baseline visit
Medications associated with a potential risk of QT prolongation, but not clearly associated with TdP	Stable dose throughout the study	Stable dose from 4 weeks prior to the baseline visit
Medications prescribed as cough suppressants (non-opioid) e.g. dextromethorphan or benzonotate	Stable Dose throughout the study	Stable dose from 14 days prior to the baseline visit
Medications prescribed for asthma, rhinitis/upper airway cough syndrome, or gastroesophageal reflux	Stable Dose throughout the study	Stable dose from 14 days prior to the baseline visit
Serotonergic drugs • serotonin reuptake inhibitors (SSRIs), • serotonin and norepinephrine reuptake inhibitors (SNRIs), • tricyclic antidepressants (TCAs), triptans, • 5-HT3 receptor antagonists, • tetracyclic antidepressants,	Stable Dose throughout the study, where possible Subjects will be informed of the risk of serotonin syndrome and the potential side effects they should be alert for, in the ICF	Stable dose from 14 days prior to the baseline visit

• 5-HT2 antagonists		
Strong inhibitors/inducers of the P450 Isozymes as per the current FDA Drug Interactions list*	Stable Dose throughout the study, where possible	Stable dose from 14 days prior to the baseline visit
Alcohol	Limit use during the study	NA

*www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

8.7. Vital signs, pulse oximetry, weight, height and BMI

The following will be recorded, prior to blood sampling wherever possible.

Vitals should be recorded with the subject in a sitting position for at least 5 minutes (except weight and height).

- Blood pressure: measured with a standard mercury sphygmomanometer, or an automated oscillometric blood pressure monitor.
- Pulse oximetry: Pulse Oximetry will be recorded with finger pulse oximeter device.
- Heart rate
- Respiratory rate
- Body temperature
- Weight
- Height: recorded at screening only, to allow the calculation of BMI.

8.8. Chest Radiograph or Computed Tomography (CT)

Chest radiograph or computed tomography (CT) of the thorax will be assessed for inclusion.

If the assessment has been performed within the last 24 months, a copy of the radiologist report is to be filed in the source as documentation of eligibility.

If not assessed in the last 24 months, or a report is not able to be obtained for review, then the procedure will be performed at screening.

8.9. Electrocardiogram (ECG)

Triplicate standard ECGs will be obtained according to the SoE. 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 3-10 minutes. Whenever possible, ECG testing should be performed prior to the collection of vital signs and blood samples (clinical laboratory and PK samples).

ECGs will be reviewed locally for safety by the Investigator and/or their designee.

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) will be assessed by the ECG specialist vendor and a report sent to site within 72 hours of successful transmission.

The screening ECG central read report will be used for the purpose of meeting the ECG study inclusion criteria.

8.10. Physical Examination

A physical examination will be performed according to the SoE. 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.

8.11. 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. Fasting is not required for routine lab tests. If medically indicated for follow-up of a certain condition or event, fasting labs can be performed.

Blood and urine samples will be collected and processed as indicated in the central laboratory manual. All blood and urine laboratory tests, except for urine pregnancy test, will be performed at the central lab. Once processed, samples will be stored for an interim period at the site before shipping to the location where the analysis will be performed. Once at the analysis location, after analysis, samples can be stored for up to 1 month, before being destroyed.

The clinical laboratory analytes described in *Table 8* will be measured at the central laboratory using consistent methodology and procedures globally at the testing locations (ICON Laboratories in Ireland and US):

Table 8 List of Laboratory Tests

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 and isoenzyme subtypes, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, carbon dioxide, creatinine, total bilirubin, gamma-glutamyl transferase, glucose, lactic dehydrogenase, Magnesium, phosphorus, potassium, sodium, total cholesterol, LDL and HDL cholesterol, total protein, and uric acid*
Urinalysis:	*Color, specific gravity, pH, glucose, ketones, protein, bilirubin, urobilinogen, blood. Microscopy will be performed on urine samples with abnormal urinalysis results.*
Coagulation:	*Prothrombin time, international normalized ratio, and activated partial thromboplastin time*
For WOCBP:	*Serum pregnancy test: betaHCG* *Urine pregnancy test: betaHCG (tested locally at site)*

8.12. Blood Sampling for Pharmacokinetics (PK)

Blood samples will be collected to determine the plasma concentrations of nalbuphine and its metabolites, Samples will be collected at the site with safety labs, according to the SoE. Further details of PK sample collection and processing will be provided in the laboratory manual. Once processed, samples will be stored for an interim period at the site, before shipping to the central

lab for forwarding to the PK lab. Samples that are sent to the PK lab can be stored for up to 5 years in case of the need for retesting for this study before being destroyed.

Plasma samples will be analyzed for nalbuphine and its metabolites using a validated liquid chromatography mass spectrometry, and reporting of concentration results will be conducted according to the current Standard Operating Procedures (SOP) at Labcorp Laboratory, Inc., Madison, Wisconsin. A bioanalytical study report will be included with the final clinical study report.

8.13. WOCBP Pregnancy test, and contraceptive counselling

For the purpose of this study, all biological females are considered to be Women of childbearing potential (WOCBP) unless they are:

- Postmenopausal; i.e., 1 year since last menses without an alternative medical or medication cause (e.g. hormonal treatments)
- Permanently sterile; i.e., Hysterectomy, Bilateral Salpingectomy, Bilateral Oophorectomy.

Women not of childbearing potential (non-WOCBP) may participate in the study without pregnancy tests and contraception requirements.

WOCBP will have urine and serum pregnancy tests as specified in the SoE regardless of sexual activity status or method of contraception. The subject must have a confirmed negative urine test prior to randomization.

WOCBP must use at least one acceptable method of birth control (if sexually active) until at least 14 days after the last dose of IP. Acceptable methods of birth control are defined in the recommendations of the Clinical Trials Facilitation and Coordination Group (*CTFG Recommendations related to contraception and pregnancy testing in clinical trials, 2020*), and for the purposes of this study are:

- Hormonal birth control for at least 3 months prior to baseline – oral, intravaginal, transdermal, injectable, or implantable,
- Intrauterine device (IUD) or or Intrauterine hormone-releasing system (IUS) in place for at least 1 month prior to baseline visit,
- Bilateral tubal occlusion (e.g. via clipping, ligation, or hysteroscopic occlusion following confirmation of full occlusion),
- Vasectomized partner,
- Barrier method – male or female condom without spermicide; cap, diaphragm or sponge with spermicide,
- Sexual abstinence - Subjects 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.

There are no contraceptive requirements for males.

8.14. Spirometry

Spirometry will be performed locally at site with a locally provided device, to assess FEV1 and FVC. Performance of spirometry should adhere to ATS/ERS guidelines (*Graham et al, 2019*).

8.15. 24-Hour Digital Cough Monitor

Measurement of cough frequency will be done using objective digital cough monitoring, the VitaloJAK®. 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, and a sensor is attached to the chest. The device has the capability to make a continuous sound recording of up to 36 hours. The device will be programed to stop recording automatically after 24-hrs. The recording is encrypted on the device and transferred electronically to the UK via a secure web portal. The digital recording is then processed through accompanying computer software, which automatically registers sound patterns typical for cough, and provides a compressed file for further analysis.

Software output provides the total number of cough events over the entire time period of recording and average hourly cough frequency and determines awake and sleep times based on the recording. The output is reviewed and analyzed by specialist analysts at the vendor. In case of poor quality, or other analyst findings, a full 24-hour manual count may be performed by specially trained individuals working under strict SOPs to ensure confidentiality of the data. Under the basis of legal obligation, sounds that may contain information that could indicate the possibility of direct harm to the participant or others may be disclosed to the principal investigator for further management under local disclosure laws. The site personnel, including the study doctor do not have access to listen to the records. 10% of readings will be reanalyzed for quality control, and variances are to be within defined limits.

At the timepoints defined in the SoE, 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 following day 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. The monitor will be returned to the site for upload of data to the vendor portal.

During the Screening Period, the cough monitor will be performed at least 10 days before the planned baseline, to allow for the analysis and results to be available prior to baseline, for inclusion in the study.

On Day 1 of the study, the monitor will be removed prior to taking the first dose of investigational product.

8.16. Patient Reported Outcome (PRO) Questionnaires

Refer to *Section 1.2 Schedule of Events, Table 2* for the overall frequency of PRO questionnaires. The questionnaires will be presented to the subject at the appropriate time as a task within the ediary provided for the purpose of the study. The details on the PROs selected are provided in Table 9.

Table 9 Patient Reported Outcome (PRO) Tools

PRO Abbreviation	PRO Full Title	Nr of Qs	Recall Period
CS-VAS	Cough Severity Visual Analog Scale	1	24 hr
LCQ©	Leicester Cough Questionnaire	19	2 weeks
PR-CF	Patient Reported Cough Frequency	1	24 hr
PGI-S Cough	Patient Global Impression of Severity – Cough	1	7 Days
PGI-C Cough	Patient Global Impression of Change – Cough	1	7 Days
SOWS	Subjective Opiate Withdrawal Scale (See *Section 8.16.1*)	16	24 hr

The recall period is the period the patient considers when responding to the questions in a PRO tool (e.g., over the last 24hr, over the last week, or since baseline).

At Baseline, PROs will be completed prior to the intake of the first dose of IP. During the study, the Patient-Reported Cough Frequency (PR-CF) will be completed daily. Other PROs will be completed at post-baseline timepoints the day after the per protocol visit date, regardless of when the actual visit is performed.

In case of premature discontinuation of IP, the IRT/e-diary system is to be updated immediately, to activate the discontinuation PROs (do not wait for the subject to come to site).

At each study visit, the PRO compliance is to be reviewed via the e-diary portal and discussed with the subject.

8.16.1. SOWS (Subjective Opiate Withdrawal Scale)

The SOWS is a self-administered scale for grading opioid withdrawal symptoms and will be collected via the e-diary. Subjects will complete the SOWS daily for 14 days, starting on (or as close as possible to) the day of stopping investigational product, whether this is at the planned end of each treatment period, or due to IP discontinuation.

Baseline SOWS will be completed to determine baseline status for relevant symptoms.

Subject reported symptoms of withdrawal captured on the SOWS will not be reported as an AE unless reported verbally as part of the overall AE assessment at each visit.

8.17. Clinical Global Impression of Severity and Change (CGI-S, CGI-C)

The CGI-S and CGI-C will be performed by the investigator.

The CGI-S is a one-item measure evaluating severity of the condition.

The CGI-C is a one-item measure evaluating change from the initiation of treatment on a seven-point scale. After 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 symptom checklists. The CGI-C can track clinical progress across time.

8.18. Randomization

A randomization schedule will be computer-generated before the start of the study. After all screening procedures are performed and results of screening tests are available, eligible subjects will be randomized in the IRT, and a blinded IP kit number will be allocated.

8.19. Telephone Contacts

At timepoints specified in the SoE, the site staff will contact the subject to support the subject with the goal of subject comfort and reducing the discontinuation rate. Activities during the phone visit include:

- Open ended questions about
  - changes to Concomitant Medication and Therapies
    (See *Section 8.6 Concomitant Medication and Therapy Assessments*)
  - changes to, or new Adverse Events
    (See *Section 7 Adverse Events and Serious Adverse Events*)
- Open ended questions about wellbeing, and a discussion on managing any concerns around titration symptoms
  (See *Section 8.21 Tolerance and Titration Symptoms Management*)
- Confirm IP intake and compliance
  (see *Section 6.4 Subject Compliance and Accountability*)
- Discussion on e-diary and PRO completion compliance, after review of the portal, as needed (see *Section 8.16 Patient Reported Outcome (PRO) Questionnaires*.

Notes on the phone call will be detailed in the source documents, and relevant information will be entered in the eCRF.

8.20. Study Drug Dispensing and Compliance Management

Refer to *Section 6 Study Treatment*, and the pharmacy manual for details on the investigational product and its management for the study.

8.21. Tolerance and Titration Symptoms Management

Systematic reviews of the literature found about 22% of patients with non-cancer pain management discontinue opioid therapy because of side effects (*McNichol, 2007*). A similar AE-related discontinuation rate for NAL ER was observed in clinical study TR12 in participants with IPF. The most frequent titration period related AEs reported with NAL ER are nausea, headache, and dizziness.

NAL ER tablets will be initiated with a titration schedule. The first dose of any new titration step will occur with an evening dose. Subjects will be educated about possible CNS AEs that may occur. If the subject misses dose/s due to titration symptoms, the Medical Monitor should be consulted to ensure all protocol allowed opportunities are used to support the participant and potentially prevent premature treatment discontinuation of the subject (see *Section 6.5 Multiple Missed Doses* for additional details).

Summarized below are the recommended options for management of side effects in those subjects that experience them. The goal is to support the subject's comfort and wellbeing through the titration period and reduce the discontinuation rate.

1. **Education and expectations** – balanced information about titration side effects should be provided. Patient material is provided to support with educating about starting NAL ER. Key points for education are:
   - There is a chance that they will experience the side effects, but also a chance they may not have any side effects during titration.
   - If they do experience side effects, there may be ways to manage these.

- For many individuals, the side effects are transient in nature.

2. **Non-medical management of Titration Symptoms –** A description of the non-medical options to manage side effects is provided in the patient material and includes recommendations like taking the medication together with a meal or snack, ginger, peppermint, and/or travel sickness acupressure bands.
3. **Medications to manage titration symptoms –**The management options in common opioid-induced adverse effects have been reviewed (*Swegle and Logemann, 2006*). One source noted that nausea was the most common opioid-related AE that patients want to avoid (*Rogers et al, 2013*). The prophylactic treatment and management of established opioid-induced nausea and vomiting has also been reviewed. (*Smith et al, 2012*).

   If subjects experience nausea and/or dizziness, Investigators are allowed to prescribe medications to manage the symptoms, as indicated for a particular subject. Subjects should be educated to start on medication in consultation with the study staff if they experience side effects. Suggested medical strategies for managing titration symptoms are:

   Nausea:
   - Prokinetic antiemetic: e.g., metoclopramide/Reglan® (metoclopramide - consider limiting dose/ frequency due to potential side effects such as dystonic reactions; avoid in any subject on concomitant SSRIs as metoclopramide can potentiate serotonin syndrome in this setting)
   - Antihistamines

   Dizziness (and associated nausea if applicable):
   - Antihistamines
   - Antimuscarinics

   Medications that should NOT be used: serotonin 5-HT3 receptor antagonist (ondansetron/Zofran®) - association with serotonin syndrome.
4. **Step down to QD dosing**: Up to and including Day 16 of either Treatment Period, if the subject is experiencing intolerable titration side effects, the subject may switch to QD dosing (i.e., skip the morning dose, and take the nighttime dose only) for 1-3 days. After the symptoms have subsided, or at the latest after 3 days, the subject is to restart BID dosing for at least 2 days. The subject can repeat the step down up to 3 times in total if symptoms return. After Day 16, the subject should have resumed consistent BID dosing, unless discussed with the Medical Monitor.

If the above steps have been tried and intolerable symptoms continue, Investigators are strongly encouraged to contact the Medical Monitor for further discussion prior to prematurely discontinuing treatment (see *Section 8.22 Premature Discontinuation / Removal of Subjects from the Trial or Study Drug* for additional details). In all cases, the Medical Monitor must be notified within 24 hours of premature discontinuation of treatment.

8.22. Premature Discontinuation / Removal of Subjects from the Trial or Study Drug

The investigator may withdraw a subject from the study for any of the following reasons:

- A significant protocol violation occurs that may adversely affect the subject's ability to remain safely in the study,
- A serious or intolerable adverse event occurs,
- A clinically significant change in a laboratory parameter occurs that may make it unsafe for the subject to continue in the study,
- The sponsor or investigator terminates the study, or
- The subject requests to be discontinued from the study.

Subjects have the right to discontinue taking study drug or withdraw from the study at any time for any reason, without prejudice to their medical care. Investigators are strongly encouraged to contact the Medical Monitor to review the reasons for a subject's discontinuation of study drug or withdrawal from the study as soon as this action is being considered by either the subject or the Investigator and before the subject stops taking study drug whenever possible, unless precluded by medical urgency. In all cases, the Medical Monitor must be notified within 24 hours after study drug or study discontinuation has occurred.

If a subject permanently discontinues the study drug for whatever reason prior to the end of the study, the following steps should be taken.

- The IRT/e-diary system is to be updated immediately, to activate the relevant PROs, especially SOWS, which should be completed from the last day of IP intake.
- Complete discontinuation procedures per the discontinuation visit schedule at the current visit OR subject to return to the site as soon as possible for the discontinuation visit, if discontinuation occurs between visits.
- The subject will be asked to return to the site for the safety follow-up visit 2 weeks after the last dose of IP.
- Ongoing SAEs will be followed until resolved, stable, or 30 days after last dose of IP, unless otherwise indicated.

If the subject withdraws consent for further study related activities at any time, then no further assessments will be performed, and the last study procedure or visit under the subject's consent will be considered End of Study. Every effort should be made to retrieve the investigational product and e-diary.

If a subject develops an acute upper respiratory tract infection (URTI) during the 21-Day Washout Period, the investigator may treat the subject as appropriate to ensure all symptoms resolve prior to the subject entering into Treatment Period 2. If necessary, the investigator should consult with the Medical Monitor prior to extending the Washout Period.

8.23. Appropriateness of Measurements

The primary efficacy and safety assessments selected are standard for clinical research in this subject population.
Boulet et al summarized the CHEST Expert Panel recommendations regarding tools to be used in clinical trials assessing cough (*Boulet et al, 2015*). The Panel recommended acoustic cough counting to assess cough frequency through objective means. The VitaloJAK has consistently

been used as the cough recorder for primary endpoint capture in trials of RCC (*McGarvey et al, 2022; McGarvey et al, 2023; Dicpinigaitis et al, 2023*).

The digital cough monitor selected is the VitaloJAK which consists of a portable sound recording device, worn in a pouch or pocket. 24-hour cough recordings are currently recognized as the standard measure of efficacy in cough studies. VitaloJAK is 510k approved in the US and has a CE Mark for EU for cough monitoring. The cough monitor is considered appropriate, as it is an objective measurement of cough frequency.

PROs were selected based on the established use in clinical trials of cough, and to cover the applicable domains of cough, breathlessness, and QOL. PROs will be performed on an electronic device (e-diary) with a CE Mark for EU.

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 & Targum 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.

Selection of safety assessments were typical of conventional medical management by pulmonologists managing this subject population, safety laboratory assessments and ECG.

9. PLANNED STATISTICAL METHODS

9.1. General Considerations

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 continuous variables directly related to cough frequency (24-hour cough frequency, sleeping cough frequency, awake cough frequency), geometric mean and geometric coefficient of variation (CV) will also be presented.

In the case that cough-frequency data are not skewed, the primary and key secondary analyses may be replicated with data that are not log-transformed. The statistical analysis plan (SAP) will contain more information on this possibility if necessary.

9.2. Incurrent Event Handling

All intercurrent events will be handled according to a "treatment policy" strategy; the collected data will be analyzed as-is. Intercurrent events may be summarized (e.g. counts of subjects who discontinue treatment) but there will be no modifications to the data or analysis based on their occurrence.

9.3. Missing Data and Dropouts

Missing data will not be imputed. Only subjects with baseline and necessary timepoint period from a given period will be eligible for summary and/or analysis for that period, and only subjects with baseline and endpoint data from both periods will be eligible for analyses that involve comparisons between treatments.

9.4. Determination of Sample Size

Assuming that subjects on placebo will experience a mean 20% reduction in 24-hour cough frequency from baseline to Day 21 and subjects on NAL ER will experience a mean 45% reduction from baseline to Day 21, the planned sample size of 48 subjects (24 per sequence) provides at least 80% power to detect a significant difference between NAL ER treatment and placebo at the 5% significance level (2-sided). This assumes a coefficient of variation (CV) of 1.12 in log-transformed Day 21 cough frequencies, which is the CV estimated from Kelsall et al, 2011 data on chronic cough in patients without esophageal catheterization.
A total of approximately 60 subjects will be randomized to ensure complete data from at least 48 subjects, assuming a 20% dropout rate.

9.5. Analysis Population

At a minimum, the following populations will be defined:

- Modified Intent-to-Treat (mITT) population: The mITT population will consist of all subjects who have received at least one dose of study drug or placebo. mITT population analyses will analyze subjects according to the treatment arm of randomization. This population will be used for non-comparative summaries of efficacy endpoints.
- Completer population: The Completer population will consist of all subjects who received at least one dose of each study drug, and for whom there is a non-missing baseline and Day 21 primary endpoint measurement in both periods. The Completer population will be used

for the primary efficacy analysis and comparative secondary efficacy analyses. (For secondary efficacy analyses, a subset of the Completer population where the appropriate endpoints for the analysis are non-missing in both periods will be used.)

- Safety population: The Safety population will consist of all subjects who have received at least one dose of study drug or placebo. Safety subjects will be analyzed according to the treatment taken; if multiple are taken, Safety subjects will be analyzed according to the highest dosage of study drug taken. This population will be used for, at minimum, analyses and summaries of adverse events, vital signs, and laboratory results.
- Pharmacokinetic (PK) population: The PK population will consist of all subjects with at least one evaluable pharmacokinetic sample. This population will be used for any summaries and analyses of PK data.
- Per Protocol (PP) population: The PP population will consist of all subjects in the mITT population who have a treatment compliance >80% and do not have a protocol deviation that excludes them from the per protocol population. A complete list of major protocol deviations that will exclude subjects from the PP population will be provided in the SAP. Subjects who are withdrawn from the study by the sponsor due to a deviation (see *Section 10.9 Protocol Violations/Deviations*) will be excluded from the PP population.

9.6. Demographics and Baseline Characteristics

Demographics and baseline characteristics, e-diary data, medical history, laboratory data, and physical examination findings will be summarized descriptively by treatment arm.

9.7. 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.

9.8. Concomitant Medication

Concomitant medications will be tabulated by Anatomical and Therapeutic Class (ATC) of World Health Organization (WHO) drug, preferred term, and treatment period. A medication's usage will be considered concomitant if it was started or continued after first administration of the study medication. Concomitant medications taken during the wash-out period between treatments will be summarized according to the treatment of the first period.

9.9. Efficacy Analyses

9.9.1. Primary Efficacy Endpoint

The primary efficacy endpoint of relative change in 24-hour cough frequency (coughs per hour) will be analyzed using a mixed-effects repeated model. This model will use log-transformed relative change in 24-hour cough frequency (log (Timepoint/ Baseline)) as the response, sequence, treatment, and time as fixed effects, the log-transformed baseline 24-hour cough frequency and sex as covariates, site as a random effect, and subject as a random repeated effect. Repeated values for subjects will be modeled using an autoregressive(1) (AR(1)) covariance. Site will attempt to be modeled using a compound symmetric covariance; however, it is expected that due to ratio of sites to subjects, this may not converge, in which case a variance components covariance structure will be used instead. In the case that a

variance components covariance structure also cannot converge, the site random effect will be removed from the model.

As a supplementary analysis, a negative binomial model will be fitted with the number of coughs as the outcome, with terms for sequence, treatment, time, and baseline cough frequency, with subject as a random effect with AR(1) covariance. As with the primary analysis, site will be treated as a random effect with compound symmetry covariance, followed by variance components covariance, followed by removing site as a random effect if convergence cannot be achieved.

As a further supplementary analysis, the primary efficacy model will be re-run separately for subjects whose baseline objective cough frequency was 10-19 coughs/hour and those whose baseline objective cough frequency was ≥20 coughs/hour.

Summaries of objective cough frequency, including change and relative change from baseline, will be provided by treatment arm. These summaries will be presented for subjects of all baseline objective cough frequencies, and also will be presented for the 10-19 coughs/hour and ≥20 coughs/hour subgroups separately.

9.9.2. Secondary Efficacy Endpoint(s)

Secondary endpoints relating to relative change from baseline to 24-hour, awake, or sleep cough frequency will be analyzed with the same mixed-effect model as for the primary endpoint, with the response and baseline covariates adjusted accordingly.

Comparisons of proportions of responders will be analyzed using a mixed-effect logistic model with the same fixed and random effects as the primary analysis. Responders will be defined as those with ≥30%, ≥50%, or ≥75% reduction in 24-hour cough frequency from baseline at Days 7, 14, or 21.

Comparisons between NAL ER and placebo for secondary efficacy endpoints that are not objective cough frequencies (CS-VAS, LCQ, PR-CF, PGI and CGI scales), summaries will be provided for Days 7, 14, and 21 as appropriate. Paired t-tests will be used for comparing mean change from baseline at each timepoint, and McNemar's test will be used for comparing binary responder proportions between NAL ER and placebo at each timepoint.

As a further supplementary analysis, the secondary efficacy endpoints will be re-run separately for subjects whose baseline objective cough frequency was 10-19 coughs/hour and those whose baseline objective cough frequency was ≥20 coughs/hour.

Secondary endpoints will not be adjusted for multiplicity and results will be taken as exploratory.

9.10. Safety Analyses

All on-treatment safety data will be assessed descriptively for AEs, SAEs, clinical laboratory measurements, vital signs, physical examinations, and SOWS. ECG data will be analyzed in a separate report by an ECG specialist vendor. The totality of these data addresses the secondary objective of characterizing the overall safety and tolerability of NAL ER in subjects with RCC. Key parameters within the overall descriptive assessment of safety and tolerability are considered to be the rate of subjects having an SAE (Safety) and the rate of subjects discontinuing due to AEs (Tolerability).

No formal statistical analysis will be performed on safety outcomes; inferences, if any, will be derived through clinical review and interpretation.

9.10.1. Adverse Events

All TEAEs will be summarized overall and for each body system and preferred term by treatment group, relationship to investigational product, and severity. TEAEs that take place prior to the first dose of the second treatment in the sequence will be summarized under the first treatment in the sequence, even if they occur during the washout period. 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. AEs will be dichotomized into "related" (definitely, probably, and possibly) and "unrelated" (unlikely and not related). "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 as well.

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 to support an eight-factor analysis. See *Section 7.2.2 Adverse Events Requiring Additional Narratives* for the list of applicable adverse events.

As cough is an endpoint in this study, it will not be reported nor analyzed as an adverse event. See *Section 9.9 Efficacy Analyses*.

9.10.2. Clinical Laboratory Assessments

Clinical safety laboratory data will be summarized descriptively by treatment group at baseline and at 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.

9.10.3. Vital Signs

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

9.10.4. Physical Examinations

Abnormal physical examination findings that suggest a clinically significant worsening from baseline will be reported as AEs 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.

9.10.5. Subjective Opiate Withdrawal Scale (SOWS)

SOWS scores will be summarized by days post-treatment and treatment group. Maximal SOWS score ($\leq$ 10, 11-20, 21-30, or > 30) and time off drug (0-1, 2, 3, 4, 5, 6, 7, or $\geq$ 8 days, calculated based on SOWS and last dose dates) will be summarized by treatment arm.

9.10.6. Electrocardiograms

Electrocardiogram data (e.g., heart rate, PR, QTcF intervals) will be presented in listings by subject and collection date/time. A complete ECG assessment will be analyzed and reported in a separate report by an ECG specialist vendor.

9.11. Pharmacokinetics (PK) and Pharmacodynamics (PD) Analysis

The study drug plasma concentration data will be provided as data listings and will also be summarized descriptively (mean, median, SD, minimum, and maximum) by nalbuphine dose/ treatment and visit.

Post-hoc pharmacokinetic analyses may be conducted through population, nonlinear mixed effects modeling; if so, this will be detailed in the SAP or in a separate post-hoc pharmacokinetic SAP.

In addition, PK-PD analyses may be conducted based on exploration of exposure-response relationships between nalbuphine plasma concentrations and efficacy parameters. These PK-PD analyses will be provided in separate ad-hoc reports if so.

Additional PK-PD analyses may be conducted to include safety and/or tolerability parameters, as appropriate.

Further details, including PK-PD modeling, will be detailed in the SAP or in a separate post-hoc pharmacokinetic SAP prior to being performed.

9.12. Other Assessments or Analyses

Additional exploratory analyses, such as examinations of the primary and some key secondary endpoints for specified subgroups, will be outlined in the SAP.

9.13. Interim Analysis

No interim statistical analyses are planned for this study.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Quality Control and Assurance

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, *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), 2018*, *CTR EU 536/2014*, and applicable regulatory requirements.

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

10.2. Investigators and Study Administrative Structure

The following will be maintained in the TMF:

- List of the CRO, laboratories, medical or technical vendors
- Coordinating Investigator details, as required by local regulations, and defined in the clinical trial application (CTA).
- List of Principal Investigators, clinical study sites, and the relevant departments.

The subject's primary care physician will be notified of the subject's participation in the study if they give permission.

10.3. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

Prior to initiation of the study, the Investigator will submit the study protocol, sample informed consent form (ICF), and other documents that pertain to subject information, recruitment methods such as subject diaries, and advertisements, according to the IRB/IEC requirements. 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.

10.4. Ethical Conduct of the Study

This study is to be conducted according to globally accepted standards of GCP (*E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), 2018*), in agreement with the latest revision of the Declaration of Helsinki, and in keeping with local regulations.

10.5. Patient Information and Consent

Refer to *Section 8.1 Informed Consent* for details on informed consent requirements and process.

10.6. Patient Confidentiality and Data Protection

Subjects will be assigned a unique identifier by the sponsor, referred to as the Participant Identification Number (PID), or unique subject ID (USUBJID). Any participant records (e.g., from the e-diary, cough monitor, labs) or datasets that are transferred to the sponsor will contain the identifier only (pseudonymized); participant names or any information which would make the participant identifiable will not be transferred. The Investigator is responsible for keeping a code list to link the subject's assigned number with identifying information. This code list will remain on site and kept in a secure manner with the study documentation, with access limited to authorized individuals.

Identifiable (non- pseudonymized) personal study-related data will be accessed by the sponsor or delegates in accordance with local data protection law. and as described in *Section 10.7 Study Monitoring* and *Section 10.10 Access to Source Documentation*. Pseudonymized data will be maintained and analyzed (see *Section 10.10 Access to Source Documentation*). Data for scientific publication will be fully anonymized

The participant will be informed in the ICF about the level of disclosure of identifiable data, including their medical records, pseudonymized, and anonymized data. The participant must be willing and able to give consent for their data to be used in this way to participate in the study.

The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. The compliance with these requirements is confirmed and documented throughout the study, starting at the initiation visit prior to the start of enrollment at any given site.

Delegated vendors (data processors) are qualified prior to use for the clinical study, via audit or other assessment, to determine the adequacy of their procedures and processes. Vendors must comply with the legal and contractual requirements, including data transfer agreements and quality agreements, where appropriate.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

In case of security breach, procedures for reporting and disclosure within the regulations and timelines of the applicable countries for the study will be followed.

10.7. 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.

10.8. Case Report Forms and Study Records

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.

10.9. Protocol Violations/Deviations

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, 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. Deviations may or may not result in the sponsor making a decision to have the subject withdrawn from the study and/or render that subject ineligible for inclusion in the Per Protocol population. The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

10.10. Access to Source Documentation

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 - Essential Documents for the Conduct of a Clinical Trial, *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), 2018*.

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.

10.11. Data Generation and Analysis

The data generated to answer the objectives of the study are:

- Objective digital cough monitor (VitaloJAK)
- Patient Reported Outcome (PRO) questionnaires
- Clinical Global Impression assessments
- Nalbuphine plasma concentrations
- For safety the objective: adverse events, clinical lab tests, vital signs, pulse oximetry, and physical examinations.

All participant data generated on site for the study will be documented in source records maintained by the site, and then entered into the CRF. Data will not be recorded directly on eCRFs. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of eCRFs and data clarification forms (DCFs) will be provided in the eCRF Completion Guidelines.

The following data are generated by the participant or by a vendor, and the vendor database is considered the source. These data will be transmitted to the sponsor or designee electronically according to Data Transfer Agreements:

- PRO questionnaires and Clinical Global Impression assessments entered directly into the e-diary interface and secure website portal;
- Cough Monitor recordings generated electronically on the device and transmitted to the Cough Monitor vendor;
- ECG recordings generated electronically on the device and transmitted to the ECG specialized vendor;
- Randomization and IP management performed directly in the IRT system.
- Laboratory samples, sent to the analyzing laboratory.

Vendor systems will generate confirmation or results reports available to site. These reports will become source data, but the source of the actions and results themselves will be the vendor database.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

10.12. Retention of Data

When the study is completed, the Investigator must retain the essential documents for 25 years to comply with regulatory guidelines before destroying the data. 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.

10.13. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The initial financial disclosure information must be provided before the site doses the first subject. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.14. Publication and Disclosure Policy

The Sponsor will retain 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. The results of the study will be posted to the publicly available website ClinicalTrials.gov independent of the outcome of the study. All proposed publications based on this study will be subject to the Sponsor's approval requirements.

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APPENDICES

LIST OF APPENDICES

Appendix 1 Sponsor Signature

Study Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Period Crossover Efficacy and Safety Study of Nalbuphine ER Tablets for the Treatment of Refractory Chronic Cough
Short Study Title	Cough Reduction in RCC with NAL ER (RIVER)
Study Number:	NAL04-201
Protocol Version	Protocol Amendment 2 19-Jun -2024

This clinical study protocol was subject to critical review and has been approved by the sponsor.

[redacted] MD
[redacted]
Trevi Therapeutics

DocuSigned by:
[redacted]
Signer Name [redacted]
Signing Reason: I approve this document
Signing Time: 19-Jun-2024 | 9:19 AM EDT
7A861C5E53044F92933590205F8920E6

Signature and Date:

Appendix 2 Investigator's Signature

Study Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Period Crossover Efficacy and Safety Study of Nalbuphine ER Tablets for the Treatment of Refractory Chronic Cough
Short Study Title	Cough Reduction in RCC with NAL ER (RIVER)
Study Number:	NAL04-201
Protocol Version	Protocol Amendment 2 19-Jun -2024

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol, and according to ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Name and Credentials _____

Job Title _____

Affiliation _____

Signature and Date _____