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

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Statistical Analysis Plan (SAP)

Protocol 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
Protocol Version No./Date:	Amendment 2.0/19-Jun-2024
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1.0 Approvals

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(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
0.1	Created as new
0.2	Second draft applying sponsor comments and updates
1.0	Applying sponsor comments and updates
1.0 revised version 03-Jul-2024	Applying sponsor comments and updates
1.0 revised version 16-Jul-2024	Stable SAP after applying sponsor updates
1.1	Applying sponsor comments and updates
1.2	Applying sponsor comments and updates after Dry Run 1
1.3	Applying sponsor comments and updates after Dry Run 2
2.0	Final SAP after applying sponsor updates

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Trevi Therapeutics, Inc. Protocol NAL04-201.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Endpoints
- Population Sets
- Conventions and Derivations
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol amendment version 2.0, 19-Jun-2024 and the case report form (CRF) v55, 04-Dec-2023. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Minor changes following this SAP will be tracked in the SAP Change Log. Final approval of this SAP by the Sponsor and ICON statistician will occur prior to database lock and unblinding of study treatment codes.

7.0 Study Objectives

7.1 Primary Objective

To assess the effect of NAL ER on 24-hour cough frequency (coughs per hour) after 21 days.

7.2 Secondary Objectives

To assess the safety and tolerability of NAL-ER for the treatment of Refractory Chronic Cough (RCC).

Explore the following efficacy, safety and tolerability related measures:

- 24-hour cough frequency (coughs per hour)
- Awake cough frequency (coughs per hour)
- Sleep cough frequency (coughs per hour)
- CS-VAS (Cough Severity Visual Analogue Scale)
- LCQ (Leicester Cough Questionnaire) total score and domain scores physical, psychological, and social domains)
- PR-CF (Patient-Reported Cough Frequency)
- PGI-S, PGI-C, Cough (Patient Global Impression of Severity and Change for Cough)
- CGI-S, CGI-C (Clinicians Global Impression of Severity and Change)

Pharmacokinetics: Assess the plasma concentrations of Nalbuphine (and/or metabolites) at all visits.

8.0 Study Design

This study is 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 Table 1 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, Table 2 Schedule of Events and Table 3 Schedule of Events for PROs.

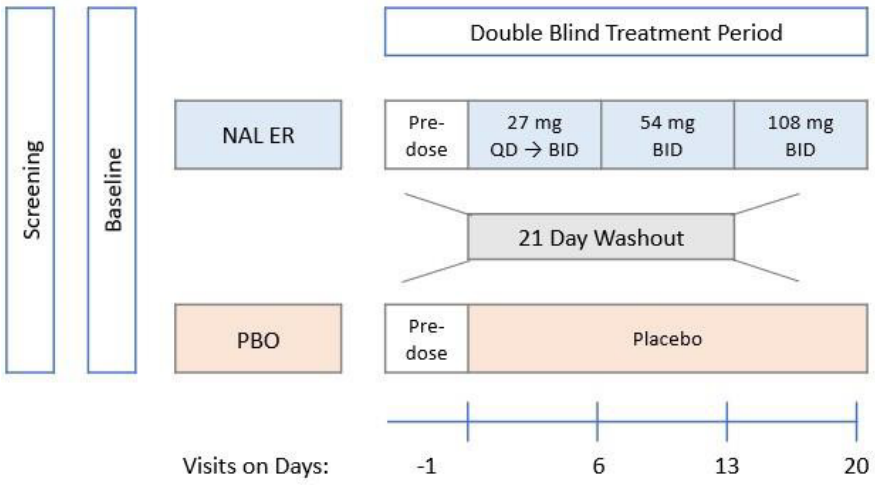
At the Screening and Baseline visits and on Days 6, 13, and 20 during each treatment period, site staff will place an electronic cough monitor on the subject, which will be worn for a 24- hour recording period to assess cough frequency. At the end of each recording session (Day 7, 14, and 21), the monitor 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.

8.1.1 Study Schematic

Figure 1 Study Schematic



8.1.2 Dosing Scheme

Table 1 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	—

8.1.3 Schedule of Events

Table 2 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 monitor 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.

8.1.4 Schedule of Events for PROs

Table 3 Schedule of Events 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 throughout 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).

8.2 Study Duration and Dates

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.

8.3 Sample Size Considerations

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)[1] 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.

8.4 Randomization and Blinding

Randomization will be performed, and blinding maintained, via Interactive Response Technology (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 24-hour objective cough frequency (coughs/hour) to a 10-19 coughs/hour subgroup and a ≥20 coughs/hour subgroup. As recruitment is predicted to be quicker for the 10-19 coughs/hour subgroup when the 10-19 coughs/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.

9.0 Study Endpoints

9.1 Primary Endpoint

The primary efficacy endpoint is relative change from Baseline in 24-hour cough frequency (coughs per hour) at Day 21 for NAL ER compared with placebo, as assessed by objective cough monitoring.

9.2 Secondary Endpoints

Objective	Endpoint
Safety and tolerability of NAL-ER for the treatment of	• Adverse events, clinical laboratory assessments, vital signs, and physical examination summaries. • ECG summaries [ECGs will be analyzed in a separate report].

Objective	Endpoint
Refractory Chronic Cough (RCC)	• 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 Cough, 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.

10.0 Population Sets

10.1 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population will consist of all subjects who are randomized and have received at least one dose of either NAL ER or placebo. mITT population analyses will analyze subjects according to the treatment arm of randomization.

10.2 Completer Population

The Completer population will consist of all subjects who received at least one dose of each NAL ER and placebo, 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 supplemental analysis of primary efficacy endpoint.

10.3 Full Analysis Set Population

The Full Analysis Set (FAS) population will consist of all subjects who received at least one dose of study drug, and for whom there is a non-missing baseline and Day 21 primary endpoint measurement in at least one treatment period. The FAS population will be used for analysis of the primary efficacy endpoint, supplemental analyses of the primary efficacy endpoint, and comparative secondary efficacy analyses as specified below.

10.4 Safety Population

The Safety (SAF) population will consist of all subjects who have received at least one dose of NAL ER or placebo. Safety subjects will be analyzed according to the treatment taken. This population will be used for analyses and summaries of demographics, adverse events, vital signs, medical history, RCC history, concomitant medications, and laboratory results.

10.5 Pharmacokinetic Population

The Pharmacokinetic (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.

11.0 Conventions and Derivations

11.1 Baseline and Change from Baseline

Unless stated otherwise, treatment period baseline will be defined as the last non-missing assessment taken, prior to the first dose of study drug for the associated treatment period (TP1 or TP2). In cases where treatment period baseline assessments are taken on the same day as the first dose of study drug and no times are reported, it will be assumed that these assessments are taken prior to study drug being administered.

If a subject is randomized but not dosed, the treatment period baseline will be defined as the last non-missing assessment prior to or on the date of randomization. For subjects completing TP1 and not treated in TP2, calculate baseline as the last non-missing assessment after last dose of TP1.

Change from baseline = (Treatment period post-baseline – Treatment period baseline)

Relative change from baseline = [(Treatment period post-baseline – Treatment period baseline) / Treatment period baseline] * 100

11.2 Study Day

The first day of the study drug administration will be defined as Day 1. In this study, the first study drug administration occurs on the day after randomization. Study day will be defined as the number of days from Day 1, with the day prior to Day 1 defined as Day -1.

Before Day 1: Study Day = (Date of interest – Date of Day 1)

On or after Day 1: Study Day = (Date of interest – Date of Day 1) + 1

11.3 24-Hour Cough Frequency

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.

The output is reviewed and analyzed by specialist analysts at the vendor. The reviewers determine the total number of cough events over the entire time period of recording, average hourly cough frequency, and the awake and sleep times based on the recording. 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.

In some cases, a subject's recording for the Day 20 cough count may take place outside of the treatment window. If a subject's cough recording for the Day 20 scheduled date takes place more than 48 hours after the subject's last dose of study drug for the treatment period, their Day 20 cough count will be considered to be missing.

11.4 Patient Reported Outcome (PRO) Questionnaires

Refer to Table 2 Schedule of Events, for the overall frequency of PRO questionnaires. The details on the PROs selected are provided below in Table 4. Patient Reported Outcome (PRO) Tools.

Table 4. Patient Reported Outcome (PRO) Tools

PRO Abbreviation	PRO Full Title	Number of items	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	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.

11.4.1 Cough Severity Visual Analog Scale (CS-VAS)

The cough severity visual analog scale (CS-VAS) is a brief, easily administered PRO that is used to assess cough severity in both acute and chronic cough. The CS-VAS is 100 mm in length and captures patients' self-assessment of cough severity ranging from 0 mm (No Cough) to 100 mm (Worst Cough Ever). See Appendix 16.1.

11.4.2 Leicester Cough Questionnaire (LCQ)

The Leicester Cough Questionnaire (LCQ) is a self-reporting quality of life measure of chronic cough. It consists of 19 items with a 7-point Likert response scale (range from 1 to 7). The responses are as follows: 1 = all the time, 2 = Most of the time, 3 = A good bit of the time, 4 = Some of the time, 5 = A little of the time, 6 = Hardly any of the time, 7 = None of the time. Each item is developed to assess symptoms during cough and impact of cough on three main domains: physical, psychological and social. LCQ total score is calculated by summing the individual scores and a higher score indicated better health status. See Appendix 16.2 and Birring et al (2003)[2].

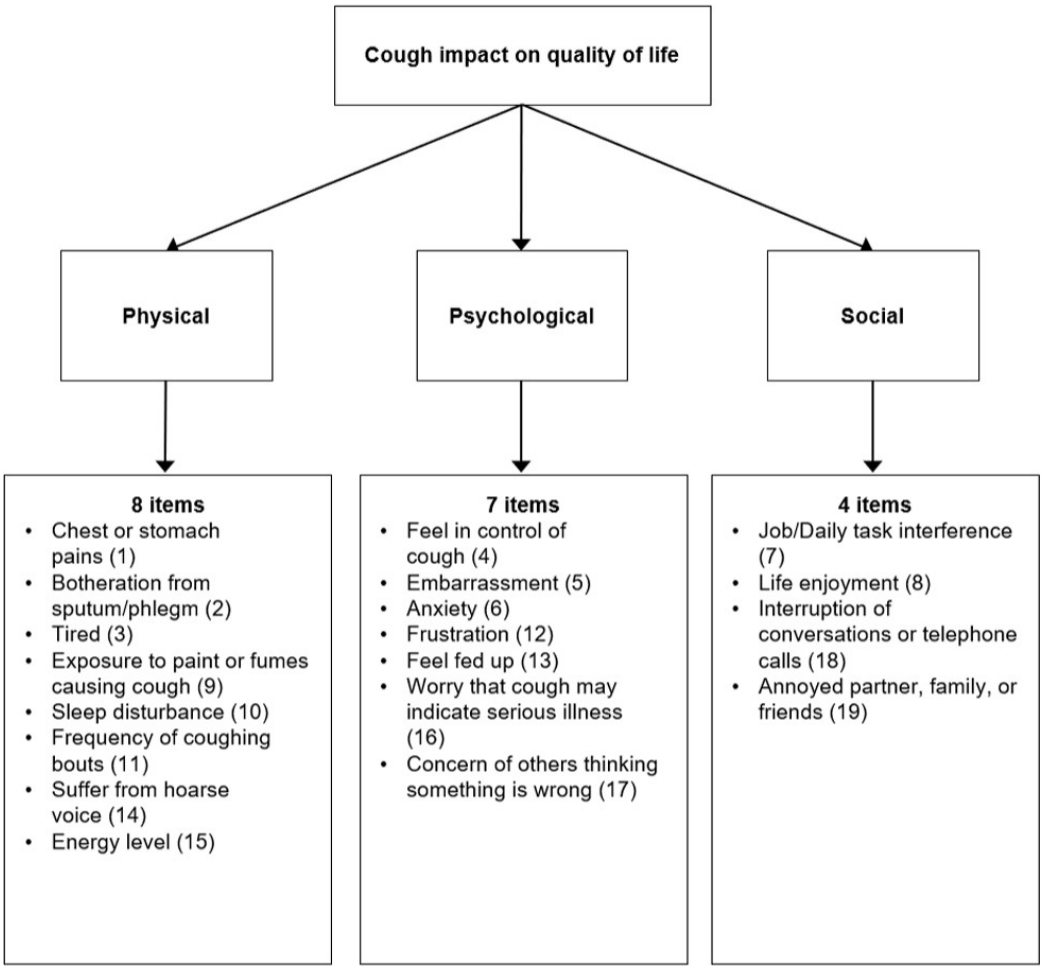
The LCQ total score, as well as the physical, psychological, and social domains as defined below will also be calculated for each time point. Questions that are included in each domain are shown in Figure 2. Domain scores are the total score from items in the domain divided by the number of items in the domain (range 1 – 7). Total scores are the sum of the domain scores (range 3 – 21).

Scoring if there are missing data will be based on the following rules;

- Physical domain: only 1 missing item allowed. (2 missing items = cannot calculate score)
- Psychological domain: only 1 missing item allowed.
- Social domain: no missing items allowed.
- Total score: always requires all 3 domain scores.

The average item score is calculated from items completed within a domain and is then used as the value for the missing items.

Figure 2: LCQ Domains



11.4.3 Patient Reported Cough Frequency (PR-CF)

Patient reported cough frequency (PR-CF) is a daily, self-reported PRO that is used to assess cough frequency. Patients rate their cough frequency over the past 24 hours using a 5-point Likert scale (0-4: 0 = Not at all, 1 = Rarely, 2 = Occasionally, 3 = Frequently, 4 = Almost Constantly).

11.4.4 Patient Global Impression of Severity and Change (PGI-S Cough, PGI-C Cough)

The Patient Global Impression of Severity – Cough (PGI-S Cough) scale is a self-reported, single-item categorical scale that is increasingly used when assessing chronic cough (CC). Patients rate the severity of their cough in the last week with a 4-point Likert scale (0-3: 0 = No Cough, 1 = Mild, 2 = Moderate, or 3 = Severe)[3].

The self-report measure Patient Global Impression of Change – Cough (PGI-C Cough) reflects a patient's belief about the efficacy of treatment. PGI-C Cough is a 7-point scale depicting a patient's rating of overall improvement over the past 7 days. Patients rate their change as “1 - Much better,” “2 - Moderately better,” “3 - A little better,” “4 - No change,” “5 - A little worse,” “6 - Moderately worse,” or “7 - Much worse.”

11.4.5 Subjective Opiate Withdrawal Scale (SOWS)

The SOWS is a self-administered test used for the assessment of opiate withdrawal symptoms. It consists of 16 items capturing symptoms rated in intensity by subjects on a 5-point scale as follows: 0 = not at all, 1= a little, 2 = moderately, 3 = quite a bit, 4= extremely. The SOWS score will be calculated as the sum of the individual scores. (See Appendix 16.5).

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

The Clinical Global Impression of Severity – Cough (CGI-S Cough) scale is an investigator-reported, single-item measure evaluating severity of the condition. Patients are rated by the severity of their cough in the last week using a 4-point Likert scale (0-3: 0 = No Symptoms, 1 = Mild, 2 = Moderate, or 3 = Severe).

The investigator reported Clinical Global Impression of Change – Cough (CGI-C Cough) scale is a single-item measure that reflects the investigator’ belief of the patient overall improvement pre-treatment baseline. Investigators rate the change in improvement as “1 - Very much improved,” “2 - Much Improved,” “3 - Minimally improved,” “4 - No change,” “5 - Minimally worse,” “6 - Much worse,” or “7 - Very much worse.”

11.6 Missing Data Analysis Methods

All intercurrent events that do not result in terminal missing data (i.e. those that have non-missing data after the intercurrent event) will be handled according to a “treatment policy” strategy; the collected data will be analyzed as-is, with no attempts to impute missing data.

For primary and secondary endpoints regarding objective cough data or the CS-VAS, intercurrent events that do result in terminal missing data (i.e. those which are following by only missing data for an endpoint) will be handled according to a “hypothetical” strategy: as these endpoints are analyzed using a mixed-effect repeated measure model, terminal missing cough data will be implicitly imputed as missing at random, under the assumption that participants with such missing data would continue to follow the trend for their treatment.

Analyses performed in the Completer population will not have terminal missing data on the primary endpoint and therefore will not contain such imputation.

For other endpoints, terminal missing data will be handled according to a “while on treatment” strategy; no terminal missing data will be imputed.

12.0 Interim Analyses

No interim statistical analyses are planned for this study.

13.0 Statistical Methods

All analyses will use SAS version 9.4 or higher.

Summary statistics will be presented by treatment group. For continuous variables, unless otherwise stated, the number of available observations (n), mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum values will be provided. Mean, median, Q1, and Q3 will be presented to 1 decimal place more than original data, standard deviation (SD) will be presented to 2 decimal places more, whilst the minimum and maximum values will match the decimal precision of the original data. For continuous variables directly related to cough frequency (24-hour cough frequency, sleeping cough frequency, and awake cough frequency), geometric mean and geometric coefficient of variation (CV) will also be presented.

In some cases, a subject's recording for the Day 20 cough count may take place outside of the treatment window. If a subject's cough recording for the Day 20 scheduled date takes place more than 48 hours after the subject's last dose of study drug for the treatment period, their Day 20 cough count will be considered to be missing.

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.

Unless otherwise noted, categorical variables will be summarized using counts and percentages and include a missing category. Percentages will be rounded to 1 decimal place with the exception of 100%, which will be displayed without any decimals. Percentages will not be displayed for zero counts. Percentages will be based on the number of subjects in the analysis set of interest (N). If the analysis is done by visits, percentages will be based on the number of subjects that have not discontinued treatment at the visit.

In listings, data will be presented with the same number of decimals as in the original data.

Titles and headers of all statistical analysis tables will indicate the corresponding study Analysis Set; the number of subjects for the Analysis Set and for each treatment will be presented in the tables.

Two-sided p-values along with 95% confidence intervals will be presented for all efficacy analyses as appropriate. Secondary endpoints will not be adjusted for multiplicity and results will be taken as exploratory. All p-values will be presented to 3 decimal places, and 95% CIs will report with the same number of decimal places as the statistics around which the confidence intervals are constructed. P-values greater than 0.999 will be presented as >0.999; p-values less than 0.001 will be presented as <0.001.

For efficacy and safety summaries, the unscheduled and repeat assessments will not be summarized; however, all results will be included in the data listings.

13.1 Subject Analysis Sets

Subject analysis sets will be summarized descriptively using the screened population and the randomized population. The number of subjects screened, and the number of screen failures will be presented. The number and percentage of subjects randomized, treated, treated with NAL ER and treated with PBO will be presented. The number and percentage of patients in each analysis set defined as defined in Section 10.0 will be presented by treatment group (for randomized population), and in total.

13.1.1 All Screened Subjects (Screened Population)

This population will consist of all subjects who were screened, whether they were considered a screen failure or not. This population will be to summarize the number of screened subjects and the number of screen failures.

13.1.2 All Randomized Subjects

This population consist of all subjects who were randomized, whether they had received study drug or not. This population will be used to summarize the randomization assignments, the subjects who received treatment, and the subject analysis sets.

Subject analysis sets will be listed.

13.2 Subject Disposition

Disposition will be summarized descriptively using the Safety population. The number and percentage of subjects who completed the study, discontinued the study, discontinued the study and completed treatment but discontinued the follow-up, discontinued the study and completed treatment and chose not to start the follow-up, completed treatment, and completed TP1 will be presented. The number and percentage of subjects who have discontinued treatment prematurely, discontinued treatment during TP1, discontinued treatment during TP2, and discontinued follow-up along with a breakdown of the corresponding reasons for discontinuation will be presented. All percentages will be calculated based on the Safety population.

Completed treatment is defined as completing both treatment periods 1 and 2.

Completed study is defined as completing both treatment periods 1 and 2 and the follow-up period.

Subject disposition will be listed.

13.3 Demographic and Screening Characteristics

Demographic data and screening characteristics will be summarized descriptively by treatment group and overall, for the Safety population.

Continuous variables including age at the time of consent, height, weight BMI at baseline, forced expiratory volume (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, duration of cough (years), screening 24-hour cough frequency, and screening cough severity VAS score will be summarized descriptively. Categorical variables including sex, race, ethnicity, and specific cough-associated medical conditions (asthma, GERD, upper airway cough syndrome (UACS)) will be summarized using frequency counts and percentages.

Demographics and screening characteristics will also be listed by patient for the Safety population.

13.4 Baseline Characteristics

Baseline characteristics will be summarized descriptively by treatment group and overall, for the FAS population.

24-hour cough frequency, awake cough frequency, sleep cough frequency, cough severity VAS score, and LCQ total, physical, psychological, and social score, will be summarized descriptively.

13.5 Medical History

Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA Version 27.0).

Medical history will be tabulated by system organ class (SOC) and preferred term (PT) using counts and percentages for the Safety population and listed by patient.

13.5.1 Refractory Chronic Cough (RCC) History

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

RCC history will be tabulated by SOC and PT using counts and percentages for the Safety population, and also listed by patient.

13.6 Treatments

13.6.1 Summary of Exposure

The duration of study drug (in days) will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption.

A summary of study drug exposure including the number and percentage of subjects receiving at least one dose and subjects with at least one dose not taken, descriptive statistics for the total number of doses expected, the total number of doses administered, and duration of exposure. Summary of exposure will be provided for the Safety population.

13.6.2 Treatment Compliance

Compliance is defined as the amount of investigational product that should have been taken by a subject based on the dosing instructions provided during a period, compared to what they are assumed to have taken, based on the number of tablets returned. Expected number of tablets will include all tablets prior to permanent study drug discontinuation, in cases where a participant early discontinues study drug. This will be expressed as percent (%) compliance.

Compliance = (Number of tablets subject actually took / Number of tablets subject was expected to take) ×100

Study drug compliance will be summarized by treatment group and overall, for the FAS population overall and by study drug. Dosing and/or compliance discrepancies (< 80%, ≥ 80% - ≤ 120%, and > 120%) will also be included and summarized by frequency counts and percentages overall and by study drug.

13.6.3 Prior and Concomitant Medications, and Procedures

Prior and Concomitant medications will be coded using WHO Drug Dictionary Enhanced version March 2024 WHODrug-Global-B3.

Any medication or therapy 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.

Prior and concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification of the WHO Drug medication group (ATC level 2) and subgroup (ATC level 4), 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. If the start date of medication is fully or partial missing, any medications will be considered to be concomitant if, based on the available date information, there is a possibility that it started on or after the first dose date. Concomitant medications taken during the wash-out period between treatments will be summarized according to the treatment of the first period.

Prior and concomitant medications will be summarized for the Safety population. The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each medication group and subgroup.

Prior and concomitant medications, and concomitant procedures will be presented in patient data listings.

13.6.3.1 Prohibited and Restricted Medications, and Washout

Subjects may receive all clinically indicated medications and therapies during the study with the exceptions noted in Table 5. Prohibited and Restricted Medications, and Washout Period.

Table 5. 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

Medication	Restriction	Washout Period
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 baseline visit
Use of a medication having a "known risk" of Torsade de Pointes (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 Torsade de Pointes	Stable Dose throughout the study	Stable doses for a full 4 weeks prior to screening and for the entirety of the study.
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, • 5-HT2 antagonists	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
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

13.7 Important Protocol Deviations

Protocol deviations noted during clinical monitoring will be documented by category (i.e., inclusion and exclusion criteria, study drug administration, study procedures and assessments, study visit schedule, informed consent, and other). All deviations will be reviewed, categorized, designated important or not important, and finalized prior to database lock. Important protocol deviations will be defined as those

potentially impacting safety or efficacy assessments and analyses. Additional details of what will be considered important can be found in the Protocol Deviation Guidance document.

Important protocol deviations for patients in the Safety population will be summarized by category. Protocol deviations will be listed.

13.8 Efficacy Analyses

All efficacy analyses will use the FAS population and for subjects on treatment unless otherwise stated. On treatment is defined as any date after the first dose date and to 48 hours past the last dose date for subjects who receive either NAL ER or placebo.

13.8.1 Analysis of Primary Efficacy Endpoint

Summaries of objective cough frequency, including change and relative change from baseline at Days 7, 14, and 21, 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.

The analyses will present the least squares mean estimates from the models along with a two-sided 95% CI tabulated for NAL ER and placebo at Day 21. The difference between the least squares mean estimates at Day 21 of NAL ER and placebo with corresponding two-sided 95% CIs and the p-values from the t-test in the model will also be presented. Additionally, analysis tables will present: the geometric mean for 24-hour cough frequency (coughs/h) at baseline and at each timepoint; the ratio of cough frequency geometric means for participants with non-missing cough frequency at both baseline and the timepoint; the model-based estimate of the geometric mean ratio and 95% confidence interval (obtained by exponentiating the model treatment estimates and confidence limits); and the relative reduction in geometric mean ratio over placebo. The relative reduction in geometric mean ratio over placebo will be calculated as 100%*[e**(Diff) - 1] where “Diff” is the model-based LS Mean estimate of the difference in log-transformed relative change from baseline at the timepoint; the confidence limits will be calculated similarly from the confidence interval of the LS Mean difference estimate.

13.8.1.1 Primary Analysis

The primary efficacy endpoint of 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 will be analyzed using a mixed-effects repeated model. This model will use log-transformed relative change in 24-hour cough frequency (log (Timepoint coughs/h / Baseline coughs/h)) as the response, sequence, time, and the treatment*time interaction 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 structure; 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. The primary efficacy analysis will use the FAS population.

13.8.1.2 Supplementary Analysis

The primary efficacy analysis will be repeated using the Completer population as a supplementary analysis.

As an additional supplementary analysis of the primary endpoint, a negative binomial model will be fitted with the number of coughs as the outcome, with terms for sequence, time, treatment*time interaction, sex, and baseline cough frequency as fixed effects, with repeated values for subject as a random repeated effect with AR(1) covariance. As with the primary analysis, site will be treated as a random effect with a compound symmetry covariance, followed by variance components covariance, followed by removing site as a random effect if convergence cannot be achieved. The model will include an offset equal to the duration of the recording in hours.

13.8.1.3 Subgroup Analyses

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. This subgroup efficacy analysis on the primary endpoint will use the FAS population. An additional supplementary analysis will repeat this subgroup analysis on the primary endpoint using the Completer population.

13.8.2 Analysis of Secondary Efficacy Endpoints

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

13.8.2.1 Secondary Analyses

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. The least squares mean estimates from the model along with a two-sided 95% CI will be tabulated for NAL ER and placebo at Day 21. The difference between the least squares mean estimates at Day 21 of NAL ER and placebo with corresponding two-sided 95% CIs and the p-values from the t-test in the model will also be presented. These analyses will use the FAS population.

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. These analyses will use the FAS population.

Comparisons between NAL ER and placebo for secondary efficacy endpoints that are not objective cough frequencies (LCQ, PR-CF, PGI-C cough and CGI-C), will be provided. PGI-S/C and CGI-S/C data are summarized by treatment arm baseline, Day7, Day 14 and Day 21 where appropriate. PR-CF are summarized by treatment arm and overall for baseline, Day7, Day 14 and Day 21. LCQ is summarized by treatment arm and overall for baseline and Day 21.

CS-VAS will be analyzed with the same mixed-effect model as for the primary endpoint, with the response and baseline covariates adjusted accordingly. The least squares mean estimates from the model along with a two-sided 95% CI will be tabulated for NAL ER and placebo at Day 21. The difference between the least squares mean estimates at Day 21 of NAL ER and placebo with corresponding two-sided 95% CIs and the p-values from the t-test in the model will also be presented. This analysis will use the FAS population.

The paired t-test is used on LCQ, PR-CF, PGI-S/C and CGI-S/C across each treatment period, to assess which treatment is more likely to result in a better subject response change from baseline at each timepoint. Ordinal scales are defined in Sections 11.4 and 11.5. Summary statistics and p-values will be presented for each timepoint. These analyses use FAS population.

McNemar's test will be used to compare binary responder proportions between NAL ER and placebo at each timepoint, using the FAS population.

13.8.2.2 Subgroup Analyses

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 using the FAS population.

13.9 Safety Analyses

All on-treatment safety data will be summarized 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 the rate of subjects having a serious adverse event (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.

13.9.1 Adverse Events

Adverse events (AEs) will be coded according to MedDRA, Version 27.0 by SOC, PT, and severity grade using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. All AE summaries will be in the Safety population.

13.9.1.1 Treatment-emergent Adverse Events (TEAEs)

Treatment-emergent adverse events are defined as starting or worsening after the first dose of study drug. Any AE will be considered to be treatment-emergent if, based on the available date information, there is possibility that it started or worsened on or after the first dose date. If the start date is missing, the event is assumed to be treatment- emergent.

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.

As cough is an endpoint in this study, it will not be reported nor analyzed as an adverse event.

An overall summary of TEAEs, including the number of events reported the number and percentage of subjects reporting at least one adverse event, subject with a ATCAE severity grade of 3 or greater, subjects discontinuing NAL ER due to an adverse event, and subjects with at least one serious adverse event, and the number and percentage of deaths will also be presented.

A breakdown of the number of events reported and the number and percentage of subjects reporting each adverse event, categorized by SOC and PT will be presented for the following:

- TEAEs
- TEAEs by maximum CTCAE severity grade
- TEAEs leading to discontinuation of NAL ER
- TEAEs related to NAL ER
- TEAEs related to NAL ER by maximum CTCAE severity grade
- TEAEs related to NAL ER leading to discontinuation of NAL ER

Relationship to IP is dichotomized into “related” (definitely, probably, and possibly) and “unrelated” (unlikely and not related) or as recorded on the CRF. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most drug-related event within that body system or preferred term.

Adverse event terms that are not found in the most current version of CTCAE will be graded according to the general guideline in Table 6 below. Subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.

Table 6. 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.

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

13.9.1.2 Treatment-emergent Adverse Events (TEAEs) Requiring Additional Narratives

The AEs listed in Table 7 will require an additional narrative in the eCRF.

The number and percentage of subjects reporting each TEAE requiring additional narratives will be summarized by SOC, PT and verbatim term.

Table 7. Adverse Events Requiring Additional Narratives

Behavioral addiction	Feeling drunk
Dependence	Hallucinations (any)
Dissociation	Intentional product misuse
Drug abuser	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	

13.9.2 Deaths and Serious Adverse Events

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, or
- a congenital anomaly/birth defect.

Although, subjects who become pregnant should be immediately discontinued from the study, pregnancy itself is not considered an adverse event or SAE. However, pregnancy information will be collected with the same process as for an SAE.

SAEs and TEAEs that lead to death will be summarized separately by SOC and PT for the Safety population.

SAEs and TEAEs that led to death be listed separately.

13.9.3 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be presented in SI units. Laboratory values of the form of “< x” (i.e., below the lower limit of quantification) or “> x” (i.e., above the upper limit of quantification) will be evaluated as “x.1” for the purpose of calculation of summary statistics and comparing to normal ranges. These values will still be displayed as “< x” or “> x” in the listings.

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 for all post-baseline values. All laboratory summaries will be presented in the Safety population.

The clinical laboratory analytes that will be measured are presented in Table 8. Marked Laboratory Abnormalities in SI Units.

Table 8. Marked Laboratory Abnormalities in SI Units

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	High
Hematology			
Hematocrit	ratio	< 0.20	> 0.55
Hematocrit	ratio		> 0.60
Hemoglobin	g/dL	< 6 g/dL	> 18 g/dL
Hemoglobin	g/dL		> 20 g/dL
Chemistry			
Total Protein	g/L		> 100 g/L
ALP	U/L		> 3X ULN
ALT	U/L		> 3X ULN
AST	U/L		> 3X ULN
ALT	U/L		> 5X ULN
AST	U/L		> 5X ULN
ALT	U/L		> 10X ULN
AST	U/L		> 10X ULN
ALT	U/L		> 20X ULN
AST	U/L		> 20X ULN
Total Bilirubin	µmol/L		> 1.5X ULN if PreTx ≤ ULN
Total Bilirubin	µmol/L		> 2X ULN if PreTx > ULN
Glucose, Plasma Unspecified	mmol/L	< 3 mmol/L	> 19.4 mmol/L
Na (Sodium)	mmol/L	< 130 mmol/L	> 150 mmol/L
Na (Sodium)	mmol/L	< 120 mmol/L	
K (Potassium)	mmol/L	≤ 2.5 mmol/L	≥ 6.0 mmol/L
Creatinine	µmol/L		≥ 1.5X PreTx CREAT
Creatinine	µmol/L		≥ 221 µmol/L
Calcium	mmol/L	< 1.88 mmol/L	≥ 0.25 mmol/L from ULN **and** ≥ 0.13 mmol/L from PreTx CA
Magnesium	mmol/L	< 0.5 mmol/L	> 2 mmol/L
PO4 (Phosphate)	mmol/L	Age 17-65: ≤ 0.58 mmol/L	Age 17-65: ≥ 1.81 mmol/L
Coagulation			
INR			>1.5

Table 9. 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 (BUN), calcium, chloride, carbon dioxide, creatinine, total bilirubin, gammaglutamyl 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, and microscopy (only on urine samples with abnormal urinalysis results
Coagulation:	Prothrombin time, international normalized ratio, and activated partial thromboplastin time
For WOCBP:	Serum pregnancy test: betaHCGa Urine pregnancy test: betaHCG

Pregnancy Testing: For patients who are women of childbearing potential (WOCBP), a urine or serum pregnancy test will be performed by the local laboratory at Screening. Pregnancy tests will also be done whenever pregnancy is suspected during the study.

The baseline laboratory value will be the Day -1 measurement taken for each period prior to the first dose of study drug for all comparisons. If a laboratory parameter was not assessed on Day -1 prior to the first dose of study drug, then the value at screening will be the baseline value.

Patients with at least 1 on-treatment measurement for each laboratory parameter will be included, where on-treatment is defined as being on or after the first dose of study treatment and not more than 30 days after the last dose of study treatment.

Clinical laboratory results will be listed by patient.

13.9.4 Vital Signs

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

Vital signs and change from baseline will be summarized in the Safety population. All vital signs and changes from baseline through the last visit will be summarized. In these tables, baseline will generally be the Day -1 measurement taken prior to any study drug administration for all comparisons. This will include a summary of the maximum and minimum values observed while the patient was on treatment and change from baseline to that observed value.

Clinically significant findings noted during screening will be reflected on the medical history CRF, while those noted during study treatment will be collected on the AE CRFs. The following vital signs will be summarized: systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), pulse rate (beats/min), body temperature (C), respiration rate (breaths/min), weight (kg) and height (cm).

Potentially clinically important vital sign results will be summarized separately. These criteria are defined as increases in blood pressure and weight changes:

- SBP (≥160 mmHg, ≥180 mmHg, ≥ 200mmHg)
- DBP (≥100 mmHg, ≥120 mmHg)

- Weight increased ≥5% from baseline
- Weight decreased ≥10% from baseline
- Temperature ≥ 38°C
- Heart rate > 100 beats/minute
- Pulse oximetry <88%

All vital signs will be listed.

13.9.5 Chest Radiograph or Computed Tomography (CT)

Chest radiograph or CT data will be listed for the Safety population.

13.9.6 Subjective Opiate Withdrawal Scale (SOWS)

SOWS scores will be summarized by number of days post-treatment and treatment group for the Safety population. Maximal SOWS score (≤ 10, 11-20, 21-30, or > 30) and time off drug (0-1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 days, calculated based on SOWS and last dose dates) will be summarized by treatment arm.

13.9.7 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.

Physical Examination data will be listed for the Safety population.

13.9.8 Electrocardiograms

Triplicate standard ECGs will be obtained according to the schedule of events. Electrocardiogram data (e.g., heart rate, PR, RR, QRS, QT, and QTc intervals) will be presented in listings by subject and collection date/time. QTc will be derived by programming using the Fridericia's formula (QTcF) using the reported values of QT (msec) and RR (msec) using the following formula:

$$\text{QTcF (msec)} = QT\ (msec) \,/\, \sqrt[3]{RR\ (msec)/1000}$$

Triplicate ECGs will be summarized. A summary of ECG parameters including heart rate (beats/min), QT interval (msec), QTcF (msec), and RR interval (msec) and change from baseline (for only QTcF) will be presented for the Safety population for each planned visit as well as the minimum, maximum, and last observation on treatment.

A summary of potentially clinically Significant QTcF values will be presented and are defined by the following categories:

- QTcF >=470 and <500 ms
- QTcF >= 500 ms
- Change in QTcF >30 ms
- Change in QTcF >60ms

For each planned visit for which a triplicate ECG is obtained, the average of the 3 values should be calculated for each parameter at each timepoint. For triplicate ECGs, baseline is defined as the mean of the set(s) of the triplicate readings on study baseline Day -1 prior to the first dose of study drug. If two sets of triplicate ECGs were obtained at baseline, then the baseline represents the mean of all ECGs. The average values will be used for the ECG tables.

A complete ECG assessment will be analyzed and reported in a separate report by an ECG specialist vendor.

13.10 Pharmacokinetic Analyses

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 for the PK population. Blood plasma nalbuphine concentration below quantifiable limit (BQL) will be set to ½ the lower limit of quantification (LLOQ).

Post-hoc pharmacokinetic analyses may be conducted through population, nonlinear mixed effects modeling; if so, this will be detailed 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. If performed, these PK-PD analyses will be provided in separate ad-hoc reports.

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 a separate post-hoc pharmacokinetic SAP prior to being performed.

13.11 Other Assessments or Analyses

13.11.1 Additional Exploratory Analyses

Additional exploratory analyses may be undertaken of the primary and some key secondary endpoints. This may include the following directions:

- Exploration of activity in subgroups based on duration of VitaloJAK recording, and subject demographic characteristics.
- Objective cough dataset analyses based on cough bout definitions, and correlations between the primary cough frequency endpoint and cough bout datasets.
- Correlations between objective cough endpoints and PRO or CGI endpoints.
- Analyses using different baseline definitions, such as use of screening results or combinations of screening and baseline periods.
- Analyses of onset of activity
- Analyses of period or sequence effect

14.0 References

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3. Rhatigan K, Hirons B, Kesavan H, et al. Patient Global Impression of Severity Scale in Chronic Cough: Validation and Formulation of Symptom Severity Categories [published online ahead of print, 2023 Sep 9]. J Allergy Clin Immunol Pract. 2023;S2213-2198(23)01007-3. doi:10.1016/j.jaip.2023.08.046
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15.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
AR	Autoregressive
ATC	Anatomic Therapeutic Classification
betaHCG	Beta human chorionic gonadotropin
BID	Twice a day (Latin: bis in die)
BMI	Body mass index
BUN	Blood urea nitrogen
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CRF	Case report form
CSR	Clinical Study Report
CS-VAS	Cough Severity Visual Analog Scale
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	diastolic blood pressure
DC	Discontinuation
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced expiratory volume
FVC	Forced vital capacity
HCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HT	Hydroxytryptamine
ICF	Informed consent form
IP	Investigational Product (Study Drug)
IRT	Interactive Response Technology for IP management
kg	Kilogram
LCQ	Leicester Cough Questionnaire

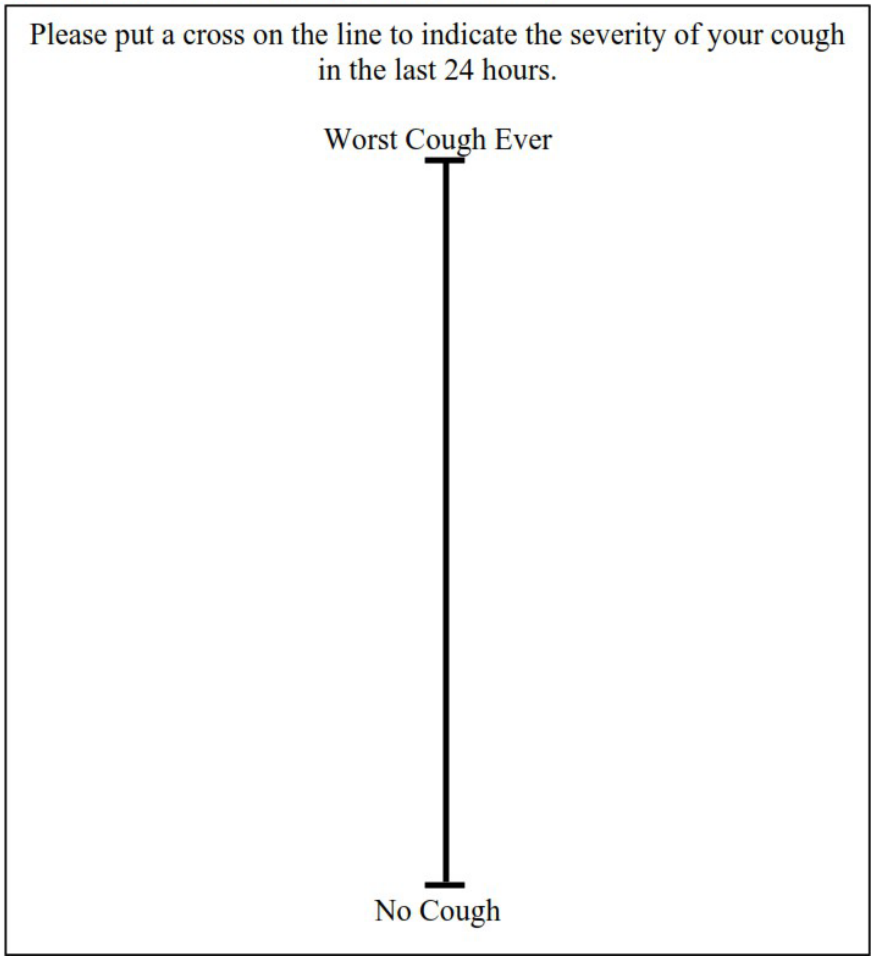
Glossary of Abbreviations:	
LDL	Low-density lipoprotein
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mITT	Modified intention-to-treat
mm	Millimeter
mmHg	Millimetres of mercury
N	Number of subjects in the analysis set of interest
n	Number of observations
NAL ER	Nalbuphine extended-release tablets
N-n	Number of missing observations
PBO	Placebo
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PR	Interval that extends from P wave onset until start of QRS complex
PR-CF	Patient-reported cough frequency
PRO	Patient reported outcome
PT	Preferred Term
QRS	Complex representing depolarization of ventricles
QT	Interval between the start of the Q wave and the end of the T wave
QTc	The corrected QT interval
QTcF	The corrected QT interval by Fridericia
RCC	Refractory Chronic Cough
RR	Time elapsed between two successive R waves of the QRS complex
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SBP	systolic blood pressure
SD	Standard deviation
SI	International System
SNRI	Serotonin and norepinephrine inhibitor
SOC	System organ class

Glossary of Abbreviations:	
SOWS	Subjective Opiate Withdrawal Scale
SSRI	Serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TEAE	Treatment-emergent adverse event
TP1	Treatment period 1
TP2	Treatment period 2
US	United States
WHO	World Health Organization
WOCBP	Women of childbearing potential

16.0 Appendices

16.1 Cough Severity Visual Analog Scale

Cough Severity Visual Analog Scale (CS-VAS)



16.2 Leicester Cough Questionnaire

LEICESTER COUGH QUESTIONNAIRE

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

	1	2	3	4	5	6	7
1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?	Every time	Most times	Several times	Sometimes	Occasionally	Rarely	Never
3. In the last 2 weeks, have you been tired because of your cough?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
4. In the last 2 weeks, have you felt in control of your cough?	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
5. How often during the last 2 weeks have you felt embarrassed by your coughing?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
6. In the last 2 weeks, my cough has made me feel anxious.	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks.	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life.	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
9. In the last 2 weeks, exposure to paints or fumes has made me cough.	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
10. In the last 2 weeks, has your cough disturbed your sleep?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
11. In the last 2 weeks, how many times a day have you had coughing attacks?	All of the time (continuously)	Most times during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	None
12. In the last 2 weeks, my cough has made me feel frustrated.	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
13. In the last 2 weeks, my cough has made me feel fed up.	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
15. In the last 2 weeks, have you had a lot of energy?	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
18. In the last 2 weeks, my cough has interrupted conversation or telephone calls.	Every time	Most times	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends.	Every time I cough	Most times when I cough	Several times when I cough	Sometimes when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

16.3 Patient Reported Cough Frequency

Patient Reported Cough Frequency (PR-CF)

Over the past 24 hours, how often did you cough?

☐ Not at all
☐ Rarely
☐ Occasionally
☐ Frequently
☐ Almost Constantly

16.4 Patient Global Impression of Severity and Change – Cough

Patient Global Impression of Cough Severity (PGI-S Cough)

How would you rate your cough over the past 7 days?

☐ No cough ☐ Mild ☐ Moderate ☐ Severe

Patient Global Impression of Change in Cough (PGI-C Cough)

Compared to when you started the study, how would you rate your cough over the past 7 days?

☐ Much better
☐ Moderately better
☐ A little better
☐ No change
☐ A little worse
☐ Moderately worse
☐ Much worse

16.5 Subjective Opiate Withdrawal Scale

Assessment of Withdrawal from Opioids

The Subjective Opiate Withdrawal Scale (SOWS)

Date ..... Time .....

		PLEASE SCORE EACH OF THE 16 ITEMS BELOW ACCORDING TO HOW YOU FEEL NOW (CIRCLE ONE NUMBER)				
	SYMPTOM	NOT AT ALL	A LITTLE	MODERATELY	QUITE A BIT	EXTREMELY
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushes	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4

Range 0-64. Handelsman, L., Cochrane, K. J., Aronson, M. J. et al. (1987)
Two New Rating Scales for Opiate Withdrawal, *American Journal of Alcohol Abuse*, 13, 293-308.

16.6 Clinical Global Impression of Severity and Change

Clinical Global Impression of Cough Severity (CGI-S-Cough)

How would you rate the subject's cough?

☐ No symptoms ☐ Mild ☐ Moderate ☐ Severe

Clinical Global Impression of Change (CGI-C)

Global Improvement: Rate total improvement whether or not in your dugjemtn it is due entirely to drug treatment. Compared to the patient's condition at admission to the project, how much has he/she changed?

☐ 1 = Very much improved
☐ 2 = Much improved
☐ 3 = Minimally improved
☐ 4 = No change
☐ 5 = Minimally worse
☐ 6 = Much worse
☐ 7 = Very much worse

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