Official Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel, 4-Arm Dose Ranging Study of the Safety and Efficacy of Nalbuphine Extended-Release Tablets (NAL ER) for the Treatment of Cough in Idiopathic Pulmonary Fibrosis (IPF)

NCT Number: NCT05964335

Document Date: Statistical Analysis Plan (Version 2.0): 20 May 2025

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Statistical Analysis Plan (SAP)

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel, 4-Arm Dose Ranging Study of the Safety and Efficacy of Nalbuphine Extended-Release Tablets (NAL ER) for the Treatment of Cough in Idiopathic Pulmonary Fibrosis (IPF)
Protocol Version No./Date:	Protocol Amendment 2 / 20-May-2024
CRF Version No./Date:	V3.0 / 03-Mar-2025
SAP Version No./Date:	V2.0 / 16-May-2025

1.0 Approvals

Sponsor	
Sponsor Name:	Trevi Therapeutics, Inc.
Representative/ Title:	[redacted], PhD, [redacted]
Signature /Date:	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document [redacted] 30346716BA9C4571A2B6FD325935FC64
Representative/ Title:	[redacted]
Signature /Date:	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-May-2025 | 15:27:13 BST
Representative/ Title:	[redacted]
Signature /Date:	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document [redacted]5 | 16:49:20 BST 7A2CEAABBAB944DB98E849776250DE2B
Representative/ Title:	[redacted]
Signature /Date:	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-May-2025 | 18:33:38 BST 0A52E5993AEB47728AF82F745312B2FB

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

ICON	
Biostatistician / Title:	[redacted], [redacted]
Signature /Date:	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-May-2025 | 19:52:24 BST
Biostatistician / Title:	[redacted]
Signature /Date:	Signed by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 20-May-2025 | 21:35:41 BST

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

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

2.0 Change History

Version/Date	Change Log
0.1	Created as new
0.2	Second draft applying Sponsor comments and updates
1.0	Final version
2.0	Updated final version

2.1 Summary of Changes from SAP version 1.0 to SAP version 2.0

Section	Item	SAP v1.0	SAP v2.0	Rationale
Signatures	Statistician	[redacted]	[redacted]	Personnel updates
Signatures	Sponsor	[redacted]	[redacted]	Personnel updates
11.5, 13.9	EXACT total score	Included in Section 13.9 (potential additional analyses)	Moved to Section 11.5 (analyses of EXACT)	Plan for inclusion in initial set of analyses
11.5	EXACT post-treatment score calculation	The post-treatment score will be defined as the mean of 7 days of scores utilizing scores from all 7 days of the target week (e.g., Days 35 to 42 for Week 6	The post-treatment score will be defined as the mean of 7 days of scores utilizing scores from all 7 days of the target week (e.g., Days 36 to 42 for Week 6	Correction of typographical error
11.5	EXACT baseline score calculation	The Baseline will be defined as the mean of 7 days of scores utilizing scores from the 7 days immediately preceding randomization (Days -7 to -1).	The Baseline will be defined as the mean of 7 days of scores utilizing scores from the 7 days immediately preceding the first study drug dose date (Days -7 to -1).	Updated to address rare situations in which start of dosing was not on the day following randomization.
11.5	EXACT post-treatment score calculation	-	If there are multiple scores on a given day within an analyses window, all scores will be included in computing the Baseline or post-treatment Visit score.	Addition of convention for special situations
11.6	CS-NRS Baseline score	-	The CS-NRS analyses will be repeated using mean of the Screening and Baseline CS-NRS to	To explore CS-NRS results utilizing an alternative baseline definition that includes both pre-dose scores (Screening and

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Section	Item	SAP v1.0	SAP v2.0	Rationale
			define the study baseline; these analyses will be considered sensitivity analysis.	Baseline) rather than just one (Baseline)
13.6.1.3	Supplementary Analyses of primary endpoint	SAS code included	SAS code removed	To ensure independent QC
13.6.2.2	Dose-Response Analysis	Plots to depict 95% CI	Plots to depict 90% CI and prediction limits	Adding prediction interval and changing interval width to match norms in dose-response analysis
13.6.3	Analysis of Secondary Endpoints	The secondary efficacy and additional variables below will be compared against placebo for each dosage using Wilcoxon rank signed tests.	The secondary efficacy and additional variables below will be compared against placebo for each dosage using Wilcoxon rank sum tests.	Correction of typographical error
Table 3	Prohibited and Restricted Medications	Serotonergic drugs	Medications that affect serotonergic neurotransmission and that when used concomitantly with opioids can increase the risk of serotonin syndrome	Alignment of serotonergic drug exclusion with protocol wording
Table 7	Marked Laboratory Abnormalities	Units for transaminase: microkat/L	Units for transaminases: U/L	Align with central laboratory units
Table 7	Marked Laboratory Abnormalities	Alkaline phosphatase <2x ULN	Removed	Correction of error (<2x ULN is not abnormal)
10.4 and 16.1	Per Protocol 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 major protocol deviation that excludes subjects from the 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 major protocol deviation or other criterion that excludes subjects from the PP population.	Not all criterion excluding subjects from the PP population were defined as major protocol deviations
13.7.8 and 9.3	Electrocardiograms	Mention of separate ECG report	Remove mention of separate ECG	No plan for separate ECG report

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Section	Item	SAP v1.0	SAP v2.0	Rationale
			report; addition of ECG tables	
13.6.1.1 and 13.6.2.1	Subgroup Analyses	Additional exploratory subgroup analyses will be performed for the primary endpoint Additional exploratory subgroup analyses will be performed for the key secondary endpoint	Additional exploratory subgroup analyses will be performed for the primary endpoint, if required. Additional exploratory subgroup analyses will be performed for the key secondary endpoint, if required.	Clarification that subgroup analyses may or may not be performed.
13.8 and 10.0	Pharmacokinetic Analyses	_	Section 13.8 removed; PK population removed.	No PK analyses will be performed under this SAP
16.1	Criteria for exclusion from per protocol population	Apply PP exclusion if PD (i.e. recording time is less than 20 hours) occurred during the Baseline, Week 6 assessment, or the early termination assessment	Apply PP exclusion if PD(i.e. recording time is less than 20 hours) occurred during the Baseline, Week 6 assessment, or the early termination assessment (based on post-QC cough duration)	Clarification of derivation of recording duration
16.1	Criteria for exclusion from per protocol population	Non-study opioid medication or opioid antagonist taken within 7 days prior to or on the day of cough recording at Baseline or Week 6.	Non-study opioid medication (other than loperamide) or opioid antagonist taken within 7 days prior to or on the day of cough recording at Baseline or Week 6.	Exclusion of loperamide from criterion because of its lack of systemic effects
16.1	Criteria for exclusion from per protocol population	Non-study opioid medication or opioid antagonist taken within 7 days prior to the first day of the Baseline, Week 6, or ET entries or on any days used for the calculation of these timepoints for the EXACT Questionnaire Q2	Non-study opioid medication (other than loperamide) or opioid antagonist taken within 7 days prior to the first day of the Baseline, Week 6, or ET entries or on any days used for the calculation of these timepoints for the EXACT Questionnaire Q2	Exclusion of loperamide from criterion because of its lack of systemic effects

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Section	Item	SAP v1.0	SAP v2.0	Rationale
16.12	Analysis Windows	-	If more than one valid assessment was performed during a Visit's analysis window, by convention, the assessment closest to the target day will be used; if both assessments are equidistant from the target day, the first assessment will be used.	Addition of convention for potential instances of more than one efficacy assessment during a Visit analysis window.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

3.0 Table of Contents

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

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 Protocol NAL03-202.

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 2, 20-May-2024 and case report form (CRF) v3.0 03-Mar-2025. 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 the SAP by Trevi Therapeutics and ICON will occur prior to database lock and unblinding of the study treatment.

7.0 Study Objectives

7.1 Primary Objective

- To assess the effect of NAL ER on 24-hour cough frequency (coughs per hour) at Week 6 using objective digital cough monitoring

7.2 Key Secondary Objective

- To assess the effect of NAL ER on the E-RS®:IPF Cough subscale (Evaluating Respiratory Symptoms in Idiopathic Pulmonary Fibrosis) as collected in the EXACT® (EXAcerbation of Chronic pulmonary disease Tool) at Week 6.

7.3 Other Secondary Objectives

The secondary objectives are to assess the following:

- Safety and tolerability of NAL ER in the study population
- 24-hour cough frequency (coughs per hour)
- Awake cough frequency (coughs per hour)
- Sleep cough frequency (coughs per hour)
- E-RS® :IPF (Evaluating Respiratory Symptoms in Idiopathic Pulmonary Fibrosis) and subscales collected in the EXACT® (EXAcerbation of Chronic pulmonary disease Tool)
- CS-NRS (Cough Severity Numerical Rating Scale)
- LCQ© (Leicester Cough Questionnaire) total score and domain scores (physical, psychological, and social domains)
- L-IPF© Impacts (Living with Pulmonary Fibrosis Impacts Questionnaire)
- L-IPF© Symptoms (Living with Pulmonary Fibrosis Symptoms Questionnaire)

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

- EQ-5D-5L™ (European Quality of Life Five Dimensions Questionnaire)
- PGI-S Cough; PGI-C Cough (Patient Global Impression of Severity and Change for Cough)
- PGI-S IPF; PGI-C IPF (Patient Global Impression of Severity and Change for IPF)
- CGI-S (Clinicians Global Impression of Severity), CGI-C (Clinicians Global Impression of Change)

8.0 Study Design

This is a multi-center randomized, double-blind, placebo-controlled, parallel, 4-arm study.

After meeting eligibility during the screening period, approximately 160 subjects with diagnosed IPF across approximately 75 centers globally will be randomized stratified by subject sex and whether subject uses antifibrotic therapy (1:1:1:1) to one of four treatment arms.

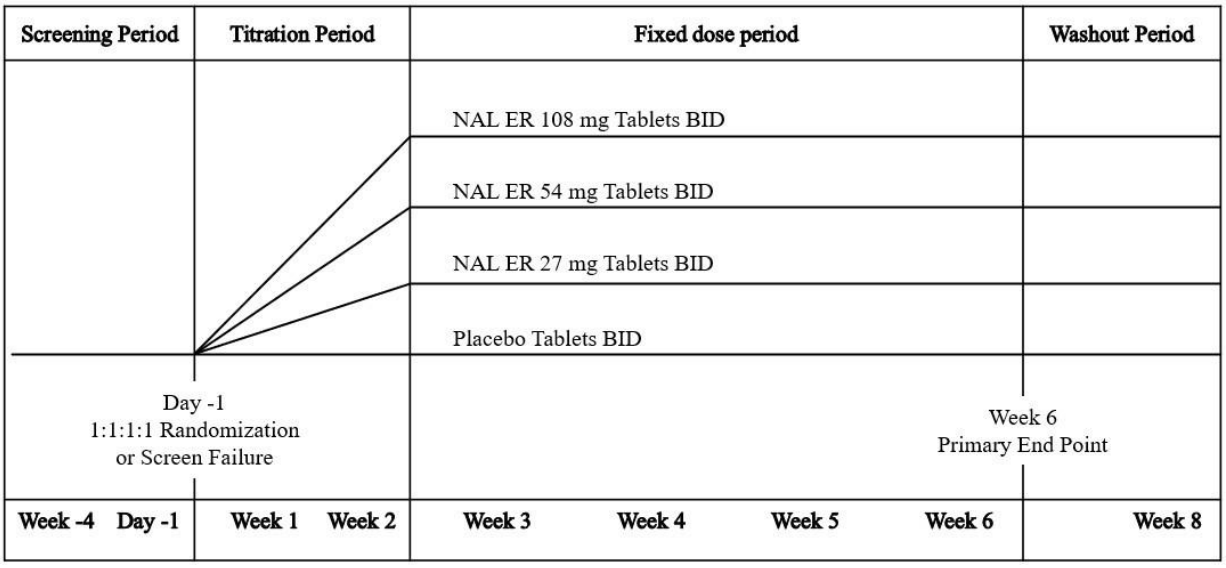
- Arm 1: Placebo
- Arm 2: 27 mg Dose Arm
- Arm 3: 54 mg Dose Arm
- Arm 4: 108 mg Dose Arm

Each arm will be titrated to their fixed dose during the blinded 2-week Titration Period according to Protocol **Table 3**, followed by the 4-week Fixed Dose Period for a total of 6 weeks on drug.

Subjects will be taken off study drug at the end of the Fixed Dose Period and followed off treatment for an additional 2 weeks. Visits and Assessments are described in Figure 1, Table 1 and Table 2.

If permanent discontinuation of study drug occurs at any time, the subject should return for a discontinuation visit and safety follow-up. They will then be contacted at Week 6 by phone to collect information on serious adverse events and vital status.

Figure 1 Study Schematic



Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Table 1 Schedule of Events

	Screening	Baseline	Titration		Fixed Dose Treatment Period		DC [8]	FU/ EOS [9]
Treatment Day/Week (visit window)	Day -28 to -2 [1]	Day -1 [2]	D4, D8 (±1 day)	W2 (D13)[3] (-2 days)	W4 (D28) (±2 days)	W6 (D42) (±2 days)	DC	W8 (+3 days)
Informed consent	X							
Demographics, Medical History, IPF History	X							
Assess subject eligibility against inclusion/exclusion criteria	X	X						
Subject Medication and Symptom Log – Dispense, Review, Re-dispense	X	X		X	X	X	X	
Record/assess AEs, Concomitant Medications, and Therapies	Continuous		☎	Throughout the Study				
Vital signs including pulse oximetry and weight [4]	X	X		X	X	X	X	X
Height, BMI	X							
Electrocardiogram (ECG) - triplicate, central over-read [4]	X	X		X		X	X	
Physical examination	X	X				X	X	
Swallow test	X							
Clinical laboratory tests [5]	X	X		X		X	X	
Pharmacokinetics (PK) blood Sample [5]		X		X	X	X	X	
Serum pregnancy test, and contraceptive counselling, if applicable	X	X						
Urine pregnancy test, and confirm result before dispensing IP		X						
Diffusing capacity of the lungs for carbon monoxide (DLCO) [6]	X							
Spirometry	X	X				X	X	
24 hr Cough monitor - Hook up, remove at home after 24 hrs [7]		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		
e-diary – PRO questionnaires, including SOWS	As described in the PRO Schedule of Events							
Clinical Global Impression of Severity (CGI-S)		X				X	X	
Clinical Global Impression of Change (CGI-C)						X	X	
Randomization		X						
IP - Dispense blister card, review dosing instructions		X		X	X			
IP - Review compliance			☎	X	X	X		
IP - Review Tolerance and manage symptoms as needed			☎	X	X	X		
Retrieve IP blister card, redispense if applicable				X	X	X	X	
Retrieve e-diary, Review and retrieve medication and symptom log								X

***AE** - Adverse Event **DC** - Discontinuation EOS - End of Study **SOWS** - Subjective Opiate Withdrawal Scale **IP** - Investigational Product **PRO** - Patient Reported Outcomes **FU** – Follow-Up*

☎ *Telephone Contact*

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

CORAL 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.

2 Baseline visit will occur on Day -1, when cough monitor will be applied. Subject will go home wearing the cough monitor. On Day 1, the subject will remove the cough monitor at home, and take their first dose of IP in the evening.

3 At Week 2, the visit will be performed on Day 13, and cough monitor removed on Day 14. Visit window can be up to 2 days before Day 13 but cannot be later.

4 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.

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

6 DLCO assessment performed in the 12 weeks prior to screening can be used for inclusion. If not available, DLCO to be performed at screening.

7 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 on Day 1 after the removal of the cough monitor.

8 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).
Contact the medical monitor if premature discontinuation is being contemplated (see protocol Section 8.23)
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 visits.
The subject will be contacted by phone at the calculated timepoint of week 6 (42 days post baseline) to collect information on serious adverse events and vital status

9 Follow-up/End of Study (EOS) will occur 14 days after last study visit, with a visit window of up to 3 days later. Last study visit can be: Week 6; Premature Discontinuation Visit; OR the last in person or phone visit, if the subject discontinues prematurely and does not consent to complete all study visits.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Table 2 Schedule of Events (SoE) for PROs

	Screening	Baseline [1]	Titration		Treatment Period				DC	FU/ EOS
Day/Week:	Day -28 to -2	Day -1	W1	W2 [2]	W3	W4 [2]	W5	W6 [2]	DC [5]	W8
EXACT	X	Daily from Day -7, and throughout the Study							H	
CS-NRS	X	X	H	H	H	H	H	H	H	
L-IPF_Impacts		X						H	H	
L-IPF_Symptoms		X						H	H	
LCQ		X						H	H	
EQ-5D-5L		X						H	H	
PGI-S Cough, PGI-S IPF	X	X		H		H		H	H	
PGI-C Cough, PGI-C IPF				H		H		H	H	
SOWS Baseline [3]		X	H				H			
SOWS: For 14 days after last dose [4]								H	H	

For full PRO Titles, refer to the protocol *EOS - End of Study* *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.
1 At Baseline, all PROs will be completed during the visit, on the day of cough monitor application.
2 At post baseline visits, PROS will be completed THE DAY AFTER the per protocol visit date, regardless of when the actual visit is performed.
3 SOWS will be completed once at Baseline, W1 and W5, to determine baseline status for relevant symptoms.
4 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 e-diary portal (do not wait for the subject to come to site).

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

8.1 Study Duration and Dates

The planned study period includes approximately 12 months recruitment period, and 3 months study period, including screening and safety follow-up.

The duration of participation for each subject will be up to 12 weeks and includes the following:

- **Screening Period**: Day -28 to Day -1. Screening should be completed within 14 days, with the possibility to extend to 28 days without rescreen for scheduling or logistical reasons.
- **Treatment Period**: Day 1 to Week 6, consisting of a 2-week blinded Titration Period continuing into the 4-week Fixed Dose Period.
- **Safety Follow-up**: 14 (±3) days after the last study treatment administration.

Actual overall study duration and/or recruitment period may vary.

8.2 Sample Size Considerations

A sample size of 28 subjects per arm will provide >80% power to detect a fold-change difference of 2.063 (relative change from baseline in the active group of 66.1% and relative change from baseline in the placebo arm of 30%) with a coefficient of variation 1.21. These estimates correspond to lognormal distributions with common standard deviation 0.95, means -1.081 and -0.357. While rigorous precautions will be taken to reduce participant discontinuation, a total of approximately 160 subjects will be randomized to account for a potential 30% dropout rate. While the primary analysis will use any available post-baseline data from participants, even those who have discontinued from the study early, clinical experience suggests that many of the early discontinuation participants will likely discontinue prior to any treatment or post-baseline assessments, so the sample size is inflated to protect against the power loss from such non-informative participants.

A Sample Size Re-Estimation (SSRE) will be performed after approximately 50% of subjects have completed Week 6 or discontinued, and the number of subjects may be adjusted up to a maximum of 400 based on the results. The SSRE will be based on the NAL 108mg arm comparison to the placebo in terms of conditional power (CP); If CP falls within the range ≥30 to <80%, sample size will be increased for the 108mg and placebo arms arm to boost power, and the 27 mg and 54 mg arms will also be equally increased in order to maintain blinding and allow for equal information gathering on all doses. If CP falls outside of this range, the study will proceed with sample size unchanged. At the maximum enrolment of 400 and with 30% dropout, there will be >80% power to detect a fold-change of 1.573 with coefficient of variation 1.21 (corresponding to relative changes from baseline of 55.5% and 30% for active and placebo).

8.3 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 1:1:1:1 ratio to either one of three NAL ER arms or placebo. Subject randomization will be stratified by subject sex and whether subject uses antifibrotic therapy.

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. See study Blinding Plan for full details on blinding for the study.

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 Week 6 for NAL ER compared with placebo.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

9.2 Key Secondary Endpoint

The key secondary efficacy endpoint is relative change from baseline in the E-RS:IPF Cough subscale at Week 6 for NAL ER compared with Placebo.

9.3 Other Secondary Endpoints

Objective	Endpoint
Safety and tolerability of NAL ER in the study population	• Adverse events • Clinical laboratory assessments • Vital signs • Spirometry • Physical examination • ECG summaries • 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 Week 2, 4, and 6, for NAL ER compared with placebo • Proportion of responders with ⩾30%, ⩾50% and ⩾75% reduction in the 24-hour cough frequency at Week 2, 4, and 6, for NAL ER compared with placebo
Awake cough frequency (Coughs per hour).	• Relative change from Baseline in awake cough frequency (coughs per hour) Week 2, 4, and 6, for NAL ER compared with placebo
Sleep cough frequency (Coughs per hour).	• Relative change from Baseline in sleep cough frequency (coughs per hour) at Week 2, 4, and 6, for NAL ER compared with placebo
E-RS®:IPF and subscales as collected in the EXACT® .	• Change from Baseline in the E-RS:IPF Cough subscale at Week 1, 2, 3, 4 and 5, for NAL ER compared with placebo • Proportion of E-RS:IPF Cough subscale responders, with response defined as at least a one category improvement at Week 1, 2, 3, 4, 5, and 6 for NAL ER compared with placebo • Change from Baseline in the E-RS:IPF total score, subdomain scores (IPF-Breathlessness, IPF-Cough, IPF-Sputum, and IPF-Chest Symptoms), and individual items at Week 1, 2, 3, 4, 5, and 6, for NAL ER compared with placebo
CS-NRS (Cough Severity Numerical Rating Scale) total score	• Change from Baseline in the CS-NRS at Week 1, 2, 3, 4, 5, and 6, for NAL ER compared with placebo
LCQ© (Leicester Cough Questionnaire) total score and response rate	• Change from Baseline in the LCQ total score at Week 6, for NAL ER compared with placebo • Proportion of LCQ total score responders, with response defined as 1.3-point increase at Week 6 for NAL ER compared with placebo • Change from Baseline in the LCQ domains and individual items at Week 6, for NAL ER compared with placebo
L-IPF© Impacts (Living with Pulmonary	• Change from Baseline in the L-IPF at Week 6, for NAL ER compared

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Objective	Endpoint
Fibrosis Impacts Module/Domain)	with placebo, utilizing both Raw Sum Scores and EAP Sum T-Scores
L-IPF© Symptoms (Living with Pulmonary Fibrosis Symptoms Module/Domain)	• Change from Baseline in the L-IPF and its domains at Week 6, for NAL ER compared with placebo, utilizing both Raw Sum Scores and EAP Sum T-Scores
EQ-5D-5L™ (European Quality of Life Five Dimensions Questionnaire)	• Change from Baseline in the EQ-5D-5L™ at Week 6, 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 Week 2, 4, and 6, for NAL ER compared with placebo • PGI-C Cough score at Week 2, 4, and 6, for NAL ER compared with placebo • Proportion of subjects with improvement by ⩾1 and ⩾2 categories, worsening by ⩾1 and ⩾2 categories, and no change on the PGI-C and PGI-S cough at each postbaseline timepoint for NAL ER compared with placebo
PGI-S IPF; PGI-C IPF (Patient Global Impression of Severity and Change for IPF)	• Change from Baseline in the PGI-S IPF at Week 2, 4, and 6, for NAL ER compared with placebo • PGI-C IPF score at Week 2, 4, and 6 for NAL ER compared with placebo • Proportion of subjects with improvement by ⩾1 and ⩾2 categories, worsening by ⩾1 and ⩾2 categories, and no change on the PGI-C and PGI-S IPF at each postbaseline timepoint for NAL ER compared with placebo
CGI-S (Clinicians Global Impression of Severity), CGI-C (Clinicians Global Impression of Change)	• Change from Baseline in the CGI-S at Week 6, for NAL ER compared with placebo • CGI-C IPF score at Week 6 for NAL ER compared with placebo • Proportion of subjects: improvement by ⩾1 and ⩾2 categories, worsening by ⩾1 and ⩾2 categories, and no change on the CGI-C and CGI-S at each post-baseline timepoint for NAL ER compared with placebo

10.0 Population Sets

10.1 Modified Intent To-Treat Population (mITT)

The mITT population will consist of all subjects who are randomized and 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 the primary, key secondary and other secondary efficacy endpoints analyses.

10.2 Safety Population (Safety)

The Safety population will consist of all subjects who have received at least one dose of study drug or

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

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 analyses and summaries of adverse events, vital signs, concomitant medications, and laboratory results.

10.3 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 major protocol deviation or other criterion that excludes subjects from the PP population. A complete list of major protocol deviations that will exclude subjects from the PP population will be provided in the Appendices 16.1. Subjects who are withdrawn from the study by the sponsor due to a deviation (see Protocol Sections 10.9) will be excluded from the PP population.

11.0 Conventions and Derivations

11.1 Baseline and Change from Baseline

The baseline value is defined as the last non-missing observation prior to the date of the first dose of study drug unless otherwise stipulated.

Change from baseline = Post-baseline – Baseline

Relative change from baseline = [(Post-baseline – Baseline) / Baseline] × 100

11.2 Study Day

Study Day 1 is defined as the date of first dose of study drug.

For dates prior to Study Day 1, the Study Day is calculated as: Study Day = (Date of Interest – Date of first dose of study drug). For dates on or post Study Day 1, Study Day = (Date of Interest – Date of first dose of study drug) + 1.

Post-treatment days is calculated as: Date of interest – date of end of treatment + 1

Time off Drug (Days) is calculated as: Date of interest – date of last dose of study drug + 1

11.3 24-Hour Cough Frequency

Measurement of cough frequency will be done using objective digital cough monitoring. The digital cough monitor consists of a portable sound recording device, which is worn in a pouch or pocket. The small microphone is clipped onto the subject's collar or lapel, as close as possible to the anterior neck, and a sensor is attached to the chest. A continuous sound recording is made for 24 hours. The digital recording is then processed through accompanying computer software, which automatically registers sound patterns typical for cough.

Software output provides the total number of cough events over the entire time period of recording and average hourly cough frequency and determines awake and sleep times based on the recording.

11.4 EQ-5D-5L

The EQ-5D-5L comprises a descriptive system with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The recall period is the day that the questions are being completed. Each of the 5 dimensions in the descriptive system has 5 levels: 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. The number and percentage of subjects at each level and for each dimension and shift from baseline will be presented by timepoint.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

11.5 EXACT© (EXAcerbation of Chronic pulmonary disease Tool); E-RS:IPF respiratory symptom subscales

The EXACT© consists of 14 items and was developed for use in chronic obstructive pulmonary disease (COPD). The E-RS:IPF consists of a subset of 11 items from the EXACT and was developed for use in IPF. The analyses will be performed utilizing methodology for the derivative scale, E-RS:IPF in its user manual: Evaluating Respiratory Symptoms (E-RS™) in Idiopathic Pulmonary Fibrosis (E-RS ™: IPF User Manual, Version 1.0 May 31, 2018)

This trial will utilize the E-RS:IPF respiratory symptom subscales and scoring systems described below. Specifically, the key secondary endpoint is based on Question 2 only of the EXACT questionnaire.

Items assignments to domains of the E-RS:IPF are as follows.

RS-Breathlessness (Items 7, 8, 9, 10, and 11); score range 0 - 23

IPF-Chest (Items 1, 5, and 6); score range 0 - 12

IPF-Cough (Item 2); score range 0 - 4

IPF-Sputum (Items 3 and 4); score range 0 – 8

E-RS:IPF total score (Items 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11); score range 0 - 47

For each day, sum the item-level raw scores to form the sub-domain score and total score.
The Baseline will be defined as the mean of 7 days of scores utilizing scores from the 7 days immediately preceding the first study drug dose date (Days -7 to -1). Four of seven scores from these 7 days are required in order to compute the mean. In situations where only 3 of 7 required scores is available, the score from Day -8 will be used, if available.

The post-treatment score will be defined as the mean of 7 days of scores utilizing scores from all 7 days of the target week (e.g., Days 36 to 42 for Week 6). Four of seven scores from these 7 days are required in order to compute the mean. In situations where only 3 of 7 required scores is available, the score from the day preceding the first day of the target week will be used, if available.

If there are multiple scores on a given day within an analyses window, all scores will be included in computing the Baseline or post-treatment Visit score.

11.6 Cough Severity-Numerical Rating Scale

The CS-NRS is a single item scale in which subjects describe the severity of their cough in the past 24 hours on a scale of 0 (no cough) to 10 (worst possible cough). The Baseline CS-NRS will be defined as the most recent pre-dose value prior to the first dose. The CS-NRS analyses will be repeated using mean of the Screening and Baseline CS-NRS to define the study baseline; these analyses will be considered sensitivity analyses.

11.7 LCQ Total and Domain Scores

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). Each item is graded on a 7-point scale: 1=all of 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. LCQ total score is calculated by summing the individual scores and a higher score indicated better health status (Birring et al 2003).

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/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)

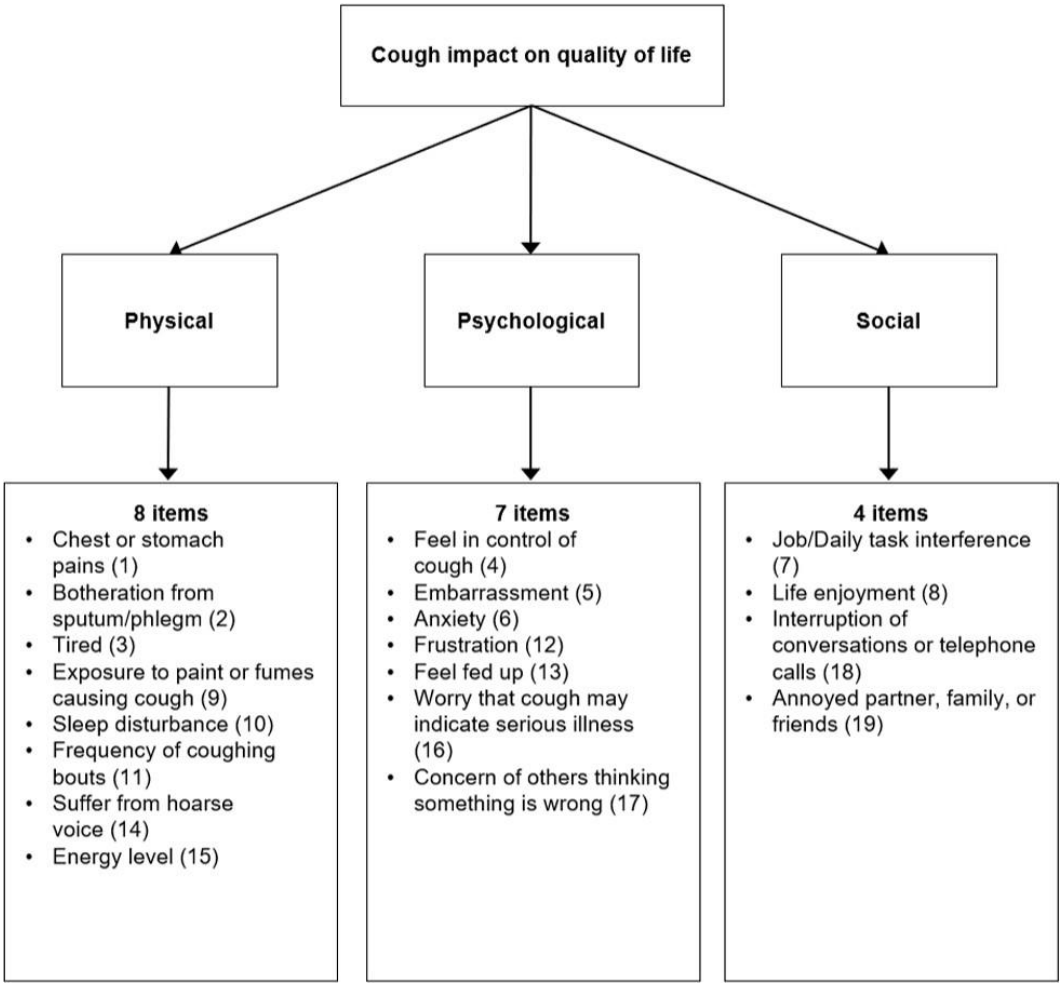
Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

- 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



11.8 PGI-S Cough and 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).

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 “-3 - Much better,” “-2 - Moderately better “-1 - A little better,” “0 - No change,” “1 - A little worse,” “2 - Moderately worse,” or “3 - Much worse.”

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

11.9 PGI-S IPF and PGI-C IPF

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

The self-report measure Patient Global Impression of Change – IPF (PGI-C IPF) reflects a patient's belief about the efficacy of treatment. PGI-C IPF is a 7-point scale depicting a patient's rating of overall improvement over the past 7 days. Patients rate their change as “-3 - Much better,” “-2 - Moderately better “-1 - A little better,” “0 - No change,” “1 - A little worse,” “2- Moderately worse,” or “3 - Much worse.”

11.10 Subjective Opiate Withdrawal Scale (SOWS) Score

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.

11.11 L-IPF©

The Living with Pulmonary Fibrosis (L-IPF) questionnaire is a 35-item questionnaire with two modules: symptoms (15 items) and impacts (20 items). Five additional questions pertaining to supplemental oxygen use are collected for descriptive purposes but are not scored.

L-IPF was developed with the input of subjects with Idiopathic pulmonary fibrosis (IPF) and thus is intended to capture perceptions specific to IPF subjects. The Symptoms module yields three domain scores: 1) dyspnea, 2) cough and 3) fatigue as well as a total Symptoms score. The Impacts module yields a single Impacts score.

The scoring method are based on the L-IPF Scoring Guide (Scoring Guide for the Living with Idiopathic Pulmonary Fibrosis (L-IPF) Questionnaire (v. Trevi 12 April 2024)).

11.11.1 L-IPF© Impacts

Scoring for the Overall Impacts Domain

Step 1: For items 1,2, and 4-15: scores equal whichever box is ticked (0-4)

Step 2:

- For items 3 and 16-20: Reverse code the items, such that:

ORIGINAL RESPONSE	0	1	2	3	4
RECODED RESPONSE	4	3	2	1	0

Step 3: For all items (1 through 20)

- Collapse response option 4 into response option 3, such that item responses range from 0 to 3

Step 4: Sum the available responses to the items

Note, if a Raw Sum Score is intended for use then stop here, this is the score.

Step 5: Convert the sum score generated in Step 3 to the corresponding Impacts EAP Sum Score or EAP Sum T-Score using Appendices 16.7.2 Score Conversion Table for the Overall Impacts Domain.

Note: Missing item responses should be handled as follows:

- Scoring should be based upon observed available data

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

- No restrictions should be imposed on scoring based on % of items with responses
- If missing is to be imputed, then multiple imputation should be invoked

11.11.2 L-IPF© Symptoms

Dyspnea (items 1-7): Dyspnea Impact Score = (sum of responses from items 1-5) × 100/20

Cough (items 8-12): Cough Impact Score = (sum of responses from items 6-10) × 100/20

Energy (items 13-15): Energy Impact Score = (sum of responses from items 12-13) × 100/8

Overall Symptoms Domain (items 1 – 15)

Scoring for the Dyspnea Domain (items 1-7):

Step1:

For items 1, 3, 4, 5 and 6:

- if “Yes” is ticked, score equals whichever box is ticked (0-4)
- if “No” is ticked and A: “I avoided this activity…” is ticked, the rating of the item is 4
- if “No” is ticked and B: “Not applicable…” is ticked, the item does not contribute to the score
- if “No” is ticked and neither “A” or “B” is ticked, the item is counted as missing and handled per general instructions for missing items (see the note below)

For item 2

- score equals whichever box is ticked (0-4)

For item 7

- if “No” is ticked, the item does not contribute to the score; otherwise, the score equals whichever box is ticked (0-4)

  Note, the five supplemental oxygen questions are informational only and do not contribute to the score

Step 2: For all items (1-7)

- Collapse response option 4 into response option 3, such that item responses range from 0 to 3

Step 3: Sum the available responses to the items

Note, if a Raw Sum Score is intended for use then stop here, this is the score.

Step 4: If a model-based score is desired, convert the sum score generated in Step 3 to the corresponding Dyspnea EAP Sum Score or EAP Sum T-Score using Appendices 16.8.2 Score conversion table for the Dyspnea domain.

Note: Missing item responses should be handled as follows:

- Scoring should be based upon observed available data
- No restrictions should be imposed on scoring based on % of items with responses
- If missing is to be imputed, then multiple imputation should be invoked

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Scoring for the Cough Domain (items 8-12):

Step 1: For all items (8-12)

- Collapse response option 4 into response option 3, such that item responses range from 0 to 3

Step 2: Sum the available responses to the items

Note, if a Raw Sum Score is intended for use then stop here, this is the score.

Step 3: Convert the sum score generated in Step 3 to the corresponding Cough EAP Sum Score or EAP Sum T-Score Appendices 16.8.3 Score conversion table for the Cough domain.

Note: Missing item responses should be handled as follows:

- Scoring should be based upon observed available data
- No restrictions should be imposed on scoring based on % of items with responses
- If missing is to be imputed, then multiple imputation should be invoked

Scoring for the Energy Domain (items 13-15):

Step 1: For items 13-15:

- Reverse code the items, such that:

ORIGINAL RESPONSE	0	1	2	3	4
RECODED RESPONSE	4	3	2	1	0

Step 2: For all items (13-15):

- Collapse response option 4 into response option 3, such that item responses range from 0 to 3

Step 3: Sum the available responses to the items

Note, if a Raw Sum Score is intended for use then stop here, this is the score.

Step 4: Convert the sum score generated in Step 3 to the corresponding Energy EAP Sum Score or EAP Sum T-Score using Appendices 16.8.4 Score conversion table for the Energy domain.

Note: Missing item responses should be handled as follows:

- Scoring should be based upon observed available data
- No restrictions should be imposed on scoring based on % of items with responses
- If missing is to be imputed, then multiple imputation should be invoked

Scoring for the Overall Symptoms Domain

Step 1: For items 1, 3, 4, 5 and 6:

- if “Yes” is ticked, score equals whichever box is ticked (0-4)
- if “No” is ticked and A: “I avoided this activity…” is ticked, the rating of the item is 4
- if “No” is ticked and B: “Not applicable…” is ticked, the item does not contribute to the score

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

- if “No” is ticked and neither “A” or “B” is ticked, the item is counted as missing and handled per general instructions for missing items (see the note below)

For item 2

- score equals whichever box is ticked (0-4)

For item 7

- if “No” is ticked, the item does not contribute to the score; otherwise, the score equals whichever box is ticked (0-4)

Note, the five supplemental oxygen questions are informational only and do not contribute to the score

Step 2: For items 13 through 15

- Reverse code the items, such that:

ORIGINAL RESPONSE	0	1	2	3	4
RECODED RESPONSE	4	3	2	1	0

Step 3: For all items (1 through 15)

- Collapse response option 4 into response option 3, such that item responses range from 0 to 3

Step 4:

- Sum the available responses to the items

Note, if a Raw Sum Score is intended for use then stop here; this is the score.

Step 5: If a model-based score is desired, convert the sum score generated in Step 4 to the corresponding Symptoms EAP Sum or EAP Sum T-Score using Appendices16.8.5 Score conversion table for the Symptoms domain.

Note: Missing item responses should be handled as follows:

- Scoring should be based upon observed available data
- No restrictions should be imposed on scoring based on % of items with responses
- If missing is to be imputed, then multiple imputation should be invoked

11.12 Missing data analysis methods

11.12.1 Primary endpoint and key secondary endpoint

- Intercurrent events of permanent treatment discontinuation or events resulting in terminal missing data:
  - “Hypothetical” strategy: The primary and key secondary endpoint will be analyzed using a mixed model for repeated measures (MMRM), which imputes data after early discontinuation or other event resulting in terminal missingness under the assumption that participants would follow the trend of their treatment group.
- Other intercurrent events, including those resulting in non-terminal missing data:
  - “Treatment policy” strategy: the collected data will be analyzed as-is and no imputation will take place for non-terminal missing data (missing data that is followed by non-missing data).

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

11.12.2 All endpoints other than the primary and key secondary endpoints

- "Hypothetical" strategy: Secondary and exploratory endpoints that are analyzed using an MMRM will follow the hypothetical strategy for intercurrent events resulting in terminal missing data, as per above.
- "While on treatment" strategy: Secondary and exploratory endpoints that are not analyzed using an MMRM will follow a while-on-treatment strategy for missing terminal data; the terminal missing data will not be imputed, and data prior to the terminal missing data will be analyzed as collected.
- "Treatment policy" strategy: Non-terminal missing data for all endpoints will not be imputed, with the collected data both prior and subsequent analyzed as-is. Intercurrent events that do not result in missing data will be analyzed using a treatment policy strategy as well, where the data following the event will not be modified or imputed if non-missing.

12.0 Interim Analyses

When approximately 50% of the subjects have either completed the Week 6 measurements or have discontinued/become lost to follow-up/otherwise ended the study early, an interim analysis of the primary endpoint for the purposes of sample size re-estimation (SSRE) will be performed. Specifications of the SSRE will be detailed in Data Monitoring Committee (DSMB) SAP. To ensure no inflation of type I error resulting from the SSRE, the primary endpoint final analysis will be based on the Cui, Hung and Wang (1999) fixed weights approach. For further information see Appendices 16.11.

13.0 Statistical Methods

All statistical procedures will be completed using SAS version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. The primary and key secondary endpoints are controlled for multiplicity while the other endpoints are not. Secondary and exploratory endpoints' p-values will be considered nominal and of limited generalizability. Two-sided 95% CI will be provided when relevant.

Continuous variables will be summarized descriptively, including number of subjects (n), mean, median, standard deviation (SD), minimum and maximum. 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. For categorical variables, summaries will include counts of subjects and percentages. Percentages will be per treatment group (e.g. the n of that treatment group is the denominator) and will be rounded to one decimal place. All summaries will be presented by treatment group and overall, unless otherwise specified.

All subject data, including those derived, will be presented in individual subject data listings without any imputation. Unless otherwise stated, unscheduled and repeat visit results will be included in subject listings only.

13.1 Subject Disposition

Subject disposition information will be summarized by treatment group and overall. The number and percentage of subjects who were screened, randomized, treated, who completed the treatment and who withdraw early from the treatment with a breakdown of the corresponding reasons for withdrawal will be presented.

The number and percentage of subjects in each analysis population with exclusions from each analysis population will be presented.

Subject disposition will be listed.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

13.2 Demographic and Baseline Characteristics

13.2.1 Demographics

Continuous variables including age at the time of consent, height, weight and BMI at baseline will be summarized descriptively. Categorical variables including sex, race and ethnicity will be summarized using frequency counts and percentages for safety population.

Demographic data will be listed.

13.2.2 Baseline and Disease Characteristics

The categorical baseline characteristics including history of cough, ability to swallow, Smoking History and GAP staging will be summarized using frequency counts and percentages for safety population. Continuous baseline variables including diffusing capacity of the lungs for carbon monoxide (DLCO) (%), forced vital capacity (FVC) (Liters), temperature (°C), systoc blood pressure (mmHg), diastolic blood pressure (mmHg), pulse oximetry (SpO2) (%), heart rate (beats/min), respiratory rate (breaths/min), GAP Index(Ley 2012) and cough duration will be summarized descriptively for safety population.

Cough duration (in days) will be calculated as: screening date – chronic cough started date + 1 day.

For chronic cough starting date, if only year is reported, impute the date to Dec 31. If the day is missing, impute it to the last day of that month.

Diagnostic testing for cough, Non-IPF respiratory conditions and past and present cough treatments will be summarized separately using frequency counts and percentages for safety population.

Baseline and disease characteristics data will be listed.

13.3 Medical History

Medical history will be coded according to Medical Dictionary for Regulatory Activities Version .1.

Medical history will be presented by system organ class (SOC) and preferred term (PT) using frequency counts and percentages for safety population.

Medical history data will be listed.

13.4 Treatment

13.4.1 Treatment Duration

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

Treatment Duration will be summarized descriptively by treatment group and total active treatment (27 mg Dose, 54 mg Dose, 108 mg Dose) for safety population.

13.4.2 Treatment Compliance

Study drug compliance will be calculated as: 100 × number of tablets subject actually took / number of tablets subject was expected to take.

Study drug compliance will be summarized by treatment group, total active treatment and overall for safety population. They will also be summarized using frequency counts and percentages in categories “≤ 50%”, >50-60%”, “>60-70%”, “>70-80%”, “>80-90%” and “> 90%”.

13.4.3 Missed Dose

Subjects with missed dose will be summarized using frequency counts and percentages by treatment group, total active treatment and overall, at each visit for safety population.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

13.4.4 Prior and Concomitant Medications

Medications will be coded by using World Health Organization (WHO) Drug Dictionary Version 2025 March. Concomitant medications are defined as those medications with a start date or continued after the date of first dose of study drug. If the start date of medication is fully or partial missing, then 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. Prohibited and restricted medications are listed in Table 3.

Prior, concomitant, prohibited and restricted medications will be summarized separately using frequency counts and percentages by Anatomical and Therapeutic Class (ATC) class and preferred name for the safety population. The N% of subjects using each class of prohibited/restricted concomitant medication, other than alcohol and strong cytochrome p450 inhibitors/inducers will be calculated by study period (14-days prior to the Baseline Visit, Titration, Treatment Period Weeks 1 – 4, Treatment Period Weks 5 – 6, and follow-up period. If a concomitant restricted/prohibited medication is missing a start date, it will be assumed to be the first administration date of treatment, and if the end date is missing, it will be assumed to be end of study or last date of subject contact, whichever comes first.

Prior and concomitant medications will be listed together while prohibited and restricted medications will be listed separately.

Table 3 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 unless required for urgent reversal of opioid adverse effects or clinical opioid overdose	14 days prior to the baseline visit
Benzodiazepines	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
Oral corticosteroid prescribed as cough treatment	Prohibited throughout the study	4 weeks prior to the baseline visit
Any other investigational product, including placebo	Prohibited throughout the study	4 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 14 days prior to the baseline visit
Medications prescribed as cough suppressants (non-opioid)	Stable Dose throughout the study	Stable dose from 14 days prior to the baseline visit
Medications that affect serotonergic neurotransmission and that when used concomitantly with opioids can increase the risk of serotonin syndrome	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

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Medication	Restriction	Washout Period
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
Anti-fibrotic medications (nintedanib and pirfenidone)	Stable Dose throughout the study	Stable dose for 8 weeks prior to the baseline visit
Alcohol	Limit use during the study	NA

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

13.5 Important Protocol Deviations

Per ICON processes, protocol deviations data will be entered into the ICON system of record Predictivv Study Operations (PSO), in accordance with the Protocol Deviation Guidance Document. Important protocol deviations are defined in the protocol deviation guidance document. The last approved version of protocol deviation guidance will be finalized before the database lock. Deviations that resulted in exclusion from the PP population will be flagged in the listing.

The number of subjects with important protocol deviations will be summarized by category of violation using frequency counts and percentages for safety population. All protocol deviations will be listed.

13.6 Efficacy Analyses

Cough-frequency data will be log transformed and may be replicated without log transformed if data are not skewed.

Efficacy analyses will be conducted for mITT.

13.6.1 Analysis of Primary Efficacy Endpoint

The primary efficacy analysis will be a mixed model repeated measures (MMRM) analysis of log-transformed relative change in hourly 24-hour cough frequency from baseline to Week 6 (log (Week 6/Baseline)) as the response variable. Fixed effect terms will include treatment group, visit, and visit by treatment group interaction; the log-transformed baseline 24-hour cough frequency, sex, and antifibrotic treatment (y/n) will also be included as covariates. Within-subject error will be modelled via a unstructured variance-covariance matrix. If the model fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity; autoregressive(1) with heterogeneity; Toeplitz, and autoregressive(1).

As described in Appendices 16.11, to avoid alpha inflation primary endpoint data generated prior to and subsequent to the planned SSRE interim analysis will be analysed separately and combined using the Cui, Hung and Wang (1999) fixed weights approach. Least Square (LS) Means and 95% CI for the mean relative change from baseline to Week 6 for each treatment group, the difference in mean log-transformed relative change from baseline to Week 6 between each active dose group versus placebo and 95% CI, p-values for treatment group comparisons (each active treatment group versus placebo) will be estimated.

The null hypotheses H_{01} and H_{02} given below will be tested against the alternative hypotheses H_{A1} and H_{A2}, respectively:

$$H_{01}: \mu_{D1} - \mu_P = 0, \quad H_{02}: \mu_{D2} - \mu_P = 0, \quad H_{02}: \mu_{D3} - \mu_P = 0,$$
$$H_{A1}: \mu_{D1} - \mu_P \neq 0, \quad H_{A2}: \mu_{D2} - \mu_P \neq 0, \quad H_{A2}: \mu_{D3} - \mu_P \neq 0,$$

where μ_{D1}, μ_{D2} and μ_{D3} denote the mean log-transformed relative change in 24-hour cough frequency from baseline to Week 6 in the three active treatment dose groups and μ_P denotes the mean log-transformed relative change in 24-hour cough frequency from baseline to Week 6 in the placebo group. D1 denotes the active treatment dose 1 group (108 mg Dose Arm), D2 denotes the active treatment dose 2 dose group (54 mg Dose Arm) and D3 denotes the active treatment dose 3 dose group (27 mg Dose Arm).

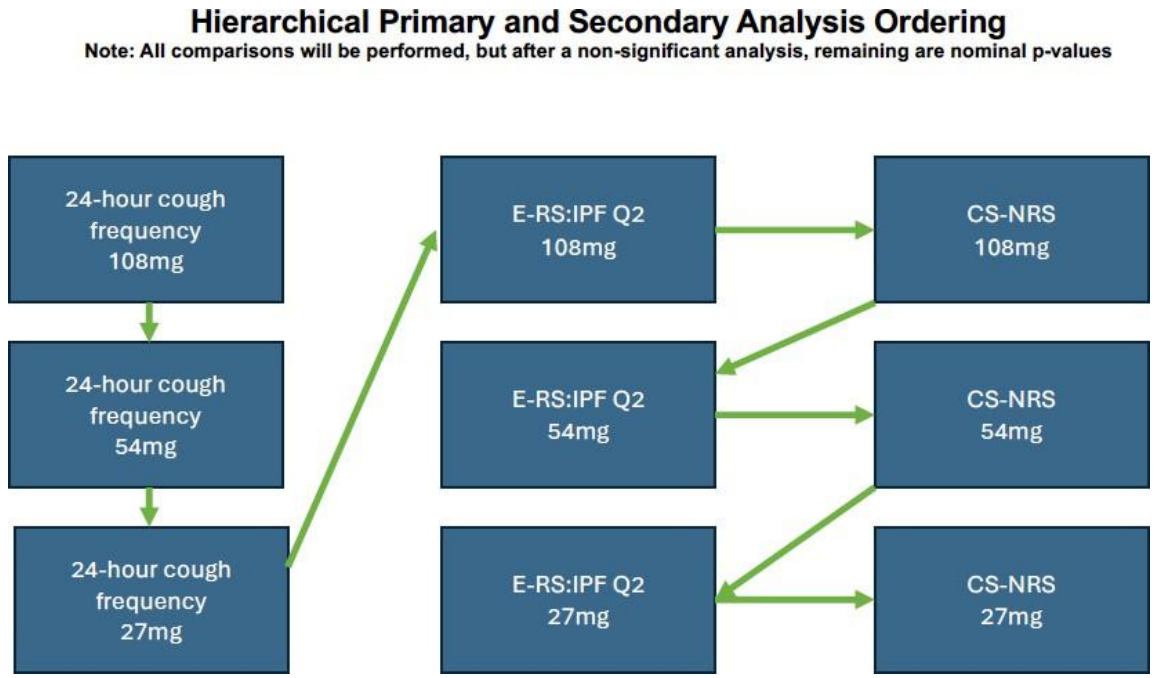
Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

The following sequential testing order will be employed to control multiplicity of testing for the primary endpoint and secondary endpoints at a family-wise Type I error rate of 0.05 (2 sided). If the first comparison is non-significant, then further comparisons will take place, but they will be considered nominal (see Figure 3).

1. Comparison of mean log-transformed relative change from baseline in 24-hour cough frequency at Week 6 between 108 mg Dose Arm and placebo.
2. Comparison of mean log-transformed relative change from baseline in 24-hour cough frequency at Week 6 between 54 mg Dose Arm and placebo.
3. Comparison of mean log-transformed relative change from baseline in 24-hour cough frequency at Week 6 between 27 mg Dose Arm and placebo.
4. Comparison of relative change from baseline in the E-RS:IPF Cough subscale at Week 6 between 108 mg Dose Arm and placebo.
5. Change from Baseline in the CS-NRS at Week at Week 6 for between 108 mg Dose Arm and placebo.
6. Comparison of relative change from baseline in the E-RS:IPF Cough subscale at Week 6 between 54 mg Dose Arm and placebo.
7. Change from Baseline in the CS-NRS at Week at Week 6 for between 54 mg Dose Arm and placebo.
8. Comparison of relative change from baseline in the E-RS:IPF Cough subscale at Week 6 between 27 mg Dose Arm and placebo.
9. Change from Baseline in the CS-NRS at Week at Week 6 for between 27 mg Dose Arm and placebo.

Figure 3 Hierarchical Primary and Secondary Analysis Ordering



Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

13.6.1.1 Subgroup Analyses

Additional exploratory subgroup analyses will be performed for the primary endpoint, if required. The specifics of these subgroup analyses will be finalized in a separate analysis plan.

13.6.1.2 Dose Response Analysis

The dose-response relationship for the primary endpoint will be explored using a 4-parameter sigmoidal Hill dose-response curve using PROC NLMIXED in SAS. The form of the fitted model shall be:

$$y = P + \frac{akD^{e^{\eta}}}{(1-k)b^{e\eta} + kD^{e\eta}} + \epsilon$$

where:

- y is the change, on the log scale, in 24-hour cough frequency (coughs/hour) from baseline to Week x post randomization [ln(24-hour coughs per hour at Week x) $-$ ln(24-hour coughs per hour at baseline) $= ln$(Week x 24h cough frequency/baseline 24h cough frequency)].
- P is basal effect
- D is log drug dose
- η is the log shape parameter
- ϵ is the random error
- a is the maximum effect (the lower asymptote is P and the upper asymptote is $a + P$ so the maximum drug effect is a)
- k is a constant where $0 < k \leq 1$
- b is the drug dose that provides an effect equal to $k \times a$
- for $k = 0.5$ then b = ED50 (the dose, which produces half of the maximum effect)
- for $k = 0.9$ then b = ED90 (the dose, which produces 90% of the maximum effect)

The parameters a, b, η and P will be estimated along with their associated standard errors and 90% and 95% 2-sided confidence intervals for k fixed at 0.5, and additionally be estimated at k=0.9.

Further, the dose-response will be plotted against dose with the response (i) on the log scale as fitted and (ii) on the back-transformed scale in terms of % change in 24-hour cough frequency (coughs/hour) from baseline to x weeks post randomization ie applying transformation of $100(e^{y} - 1)$ together with 90% 2-sided confidence and prediction limits.

13.6.1.3 Supplementary Analyses

The supplementary analysis will be a negative binomial model with total 24-hour cough frequency as the response variable. Fixed effect terms will include treatment group, visit, and visit by treatment group interaction, sex, and antifibrotic treatment (y/n) will also be included as covariates.

13.6.2 Analysis of Key Secondary Efficacy Endpoint

The key secondary efficacy analysis will be an MMRM of relative change from baseline in the E-RS:IPF Cough subscale to Week 6 as the response variable. Fixed effect terms will be included for treatment group, visit, and visit-by-treatment group interaction; baseline E-RS:IPF Cough subscale, sex, and a antifibrotic treatment (y/n) will be included as covariates in the model. Within-subject error will be modeled via a unstructured variance-covariance matrix. If the model fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity; autogressive(1) with heterogeneity; Toeplitz, and autoregressive(1).

In the event that the model diagnostics for the MMRM suggest that the model assumptions are not met by the key secondary endpoint, a non-parametric analysis will be employed as an additional supplementary analysis. In this case, change from baseline at week 6 in E-RS:IPF Cough subscale will be analyzed using

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

a Mann-Whitney U test. Change from baseline in E-RS:IPF Cough subscale will still be summarized at each week in this case, and the U test statistic and p-value will be reported for the Week 6 results.

LS Means and 95% CI for the mean relative change for each treatment group, the difference in mean relative change from baseline to Week 6 between each active dose group versus placebo and 95% CI, p-values for treatment group comparisons (each active treatment group versus placebo) will be provided (see Figure 3).

13.6.2.1 Subgroup Analyses

Additional exploratory subgroup analyses will be performed for the key secondary endpoint, if required. The specifics of these subgroup analyses will be finalized in a separate analysis plan.

13.6.2.2 Dose Response Analysis

The dose-response relationship for the key secondary endpoint will be analyzed by the same method as the primary endpoint in section 13.6.1.2, with the response altered to match the key secondary endpoint (i.e. relative change from baseline in E-RS:IPF Cough subscale score with no log transformation).

Further, the dose-response will be plotted against dose with the response (relative change from baseline in E-RS:IPF Cough subscale score with no log transformation) as fitted and from baseline to x weeks post randomization together with 90% 2-sided confidence and prediction limits.

13.6.3 Analysis of Secondary Efficacy Endpoints

The secondary efficacy variables below will be analyzed using the same MMRM for the primary endpoint detailed in Section 13.7.1. No hierarchical testing will be performed and any presented p-values will be considered nominal and of limited generalizability.

- Relative change from Baseline in 24-hour cough frequency (coughs per hour) at Week 2 and 4 for NAL ER compared with placebo.
- Relative change from Baseline in awake cough frequency (coughs per hour) Week 2, 4, and 6, for NAL ER compared with placebo.
- Relative change from Baseline in sleep cough frequency (coughs per hour) at Week 2, 4, and 6, for NAL ER compared with placebo.

The secondary efficacy variables below will be analyzed using the same MMRM for the key secondary endpoint detailed in Section 13.7.2; no hierarchical testing will be performed.

- Change from Baseline in the E-RS:IPF Cough subscale at Week 1, 2, 3, 4 and 5, for NAL ER compared with placebo.

The secondary efficacy and additional variables below will be analyzed using a mixed-effects logistic regression of below-defined responder (0,1) as the response variable, with treatment group, visit, and treatment-by-visit interaction as fixed effects and log-transformed baseline 24-hour cough frequency, sex, and antifibrotic treatment (y/n) as covariates in the model. Odds ratios (each active treatment group versus placebo) with 95% CIs and p-values will be provided. Within-subject covariance will use the same algorithm as the key secondary analysis.

- Proportion of responders with ≥ 30%, ≥ 50% and ≥ 75% reduction in the 24-hour cough frequency at Week 2, 4, and 6, for NAL ER compared with placebo.
- Proportion of E-RS:IPF Cough subscale responders, with response defined as at least a one category improvement at Week 1, 2, 3, 4, 5, and 6 for NAL ER compared with placebo.
- Proportion of subjects with improvement by ≥1 and ≥2 categories, worsening by ≥1 and ≥2 categories, and no change on the PGI-C and PGI-S cough at each post-baseline timepoint for NAL ER compared with placebo. For the PGI-C, a 1-category improvement would mean choice at a given timepoint of “a little better”, a 2-category improvement would mean a choice of “moderately better”.
- Proportion of subjects with improvement by ≥1 and ≥2 categories, worsening by ≥1 and ≥2

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

categories, and no change on the PGI-C and PGI-S IPF at each post-baseline timepoint for NAL ER compared with placebo. For the PGI-C, a 1-category improvement would mean choice at a given timepoint of “a little better”, a 2-category improvement would mean a choice of “moderately better”.

- Proportion of subjects: improvement by ≥1 and ≥2 categories, worsening by ≥1 and ≥2 categories, and no change on the CGI-C and CGI-S at each post-baseline timepoint for NAL ER compared with placebo. For the CGI-C, a 1-category improvement would mean choice at a given timepoint of “minimally improved”, a 2-category improvement would mean a choice of “much improved”.

The secondary efficacy and additional variables below will be compared against placebo for each dosage using Wilcoxon rank sum tests. Treatment difference of the mean change from baseline between each active dose group versus placebo with 95% CI and p-values will be provided. For the L-IPF, both the raw sum scores and the EAP sum T-scores will be calculated.

- Change from Baseline in the E-RS:IPF sub-domains, total score and individual items at Week 1, 2, 3, 4, 5, and 6, for NAL ER compared with placebo.
- Change from Baseline in the CS-NRS at Week 1, 2, 3, 4, and 5 , for NAL ER compared with placebo.
- Change from Baseline in the LCQ© total score at Week 6, for NAL ER compared with placebo.
- Change from Baseline in the LCQ© domains (physical, social, and psychological) at Week 6, for NAL ER compared with placebo.
- Change from Baseline in the L-IPF© Impacts Module/Domain at Week 6, for NAL ER compared with placebo, utilizing both Raw Sum Scores and EAP Sum T-Scores.
- Change from Baseline in the L-IPF© Symptoms Module/Domain (including Dyspnea, Cough, Energy, and Overall Symptoms Domains) at Week 6, for NAL ER compared with placebo, utilizing both Raw Sum Scores and EAP Sum T-Scores.
- Change from Baseline in the PGI-S Cough; PGI-C Cough at Week 2, 4, and 6, for NAL ER compared with placebo.
- Change from Baseline in the PGI-S IPF; PGI-C IPF at Week 2, 4, and 6, for NAL ER compared with placebo.
- Change from Baseline in the CGI-S, CGI-C at Week 6, for NAL ER compared with placebo.

The secondary efficacy variables below will be compared against placebo for each dosage using chi-square tests. The odds ratio (each active treatment group versus placebo) with 95% CI and p-value will be provided.

- Proportion of LCQ© responders, with response defined as 1.3-point increase at Week 6 for NAL ER compared with placebo.

13.7 Safety Analyses

Safety analyses will be conducted on all data collected during the treatment period for safety population.

All safety data will be summarized by treatment group and total active treatment (i.e. total for 27 mg, 54 mg, 108 mg).

The safety analyses of change from baseline to a specific visit in safety variables (e.g., laboratory parameters, vital signs) will only include subjects who have data available for both the baseline and the visit under consideration unless otherwise specified.

No statistical tests will be performed.

13.7.1 Adverse Events

Adverse events (AEs) will be coded according to MedDRA, Version 28.0 by SOC, PT, and severity grade using Common Terminology Criteria for Adverse Events (CTCAE) Version 6.0.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

13.7.1.1 Treatment-emergent Adverse Events (TEAEs)

Treatment-emergent adverse events is defined as starting or worsening on or 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 on or after the first dose date. If the start date is missing, the event is assumed to be treatment-emergent unless the end date is before the first dose of study drug. Relationship to IP is dichotomized into “related” (definitely, probably, and possibly) and “unrelated” (unlikely and not related).

An overall summary of TEAEs including the number of events reported, the number and percentage of subjects will be presented. A breakdown of the number of events reported, the number and percentage of subjects reporting each adverse event categorized by SOC and PT will be presented. Subjects are only counted once within each SOC or PT at the maximum severity.

The following summaries will be presented:

- TEAEs
- Related TEAEs
- TEAEs by maximum CTCAE severity grade
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- Death

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

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

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
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	

The number and percentage of subjects reporting each TEAE requiring additional narratives categorized by SOC and PT will be presented.

13.7.2 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.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

SAE and TEAEs that lead to death will be summarized separately by SOC and PT.

SAE and TEAEs that led to death be listed separately.

13.7.3 Laboratory Data

For the purposes of summarization in both the tables and listings, all laboratory values will be presented in SI units. If a lab value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier.

Laboratory parameters will be summarized descriptively by treatment group and total active treatment at baseline and each scheduled visit. Summaries 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 be listed. Listings will include scheduled, unscheduled, and repeat evaluations. A listing of markedly abnormal values, as defined below, will additionally be provided. For each subject with a marked abnormality (MA) for a parameter, all the subject's values for that parameter will be listed.

The clinical laboratory analytes that will be measured are presented in Table 5.

Table 5 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, and microscopy (only on urine samples with abnormal urinalysis results)
Coagulation:	Prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time
For Women of Childbearing Potential (WOCBP):	Serum pregnancy test: beta-HCGa Urine pregnancy test: beta-HCG

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Marked laboratory abnormalities

Laboratory abnormalities will be evaluated based on MA values. The pre-defined criteria for marked abnormalities are detailed in Table 6 and Table 7. If both the baseline and post-baseline values of a parameter are beyond the same MA limit for the parameter, then the post-baseline value will be considered an MA only if it is more extreme (farther from the limit) than was the baseline value. If the baseline value is beyond the low MA limit, and the post-baseline value is beyond the high MA limit (or vice-versa), then the post-baseline value will be considered a MA.

Table 6 Marked laboratory abnormalities in SI unis

Clinical Laboratory variables	Units	Marked Abnormality Criteria	
		Low	High
Hematology			
Hematocrit	ratio	< 0.20	> 0.55
Hematocrit	ratio		> 0.60
Hemoglobin	g/dL	< 8 g/dL	> 18 g/dL
Hemoglobin	g/dL		> 20 g/dL
Chemistry			
Total Protein	g/L		> 100 g/L
ALP	U/L		> 3X ULN
ALP	U/L		
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

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Table 7 Marked laboratory abnormalities in conventional units

Clinical Laboratory variables	Conventional Units	Marked Abnormality Criteria	
		Low	High
Hematology			
Hematocrit	%	< 20	> 55
Hematocrit	%		> 60
Hemoglobin	g/dL	< 8 g/dL	> 18 g/dL
Hemoglobin	g/dL		> 20 g/dL
Chemistry			
Total Protein	g/dL		> 10 g/dL
ALP	U/L		> 3X ULN
ALP	U/L		
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	mg/dL		> 1.5X ULN if PreTx ≤ ULN
Total Bilirubin	mg/dL		> 2X ULN if PreTx > ULN
Glucose, Plasma Unspecified	mg/dL	< 54.1 mg/dL	> 394.5 mg/dL
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	mg/dL		≥ 1.5X PreTx CREAT
Creatinine	mg/dL		≥ 2.5 mg/dL
Calcium	mg/dL	< 7.54 mg/dL	≥ 1 mg/dL from ULN **and** ≥ 0.52 mg/dL from PreTx CA
Magnesium	mEq/L	< 1 mEq/L	> 4 mEq/L
PO4 (Phosphate)	mg/dL	Age 17-65: ≤ 1.8 mg/dL	Age 17-65: ≥ 5.61 mg/dL
Coagulation			
INR			>1.5

13.7.4 Vital Signs

Vital sign measurements (systolic blood pressure, diastolic blood pressure, heart rate, temperature, SpO2, respiration rate, and weight) will be summarized descriptively by treatment group and total active treatment at baseline and each scheduled visit.

Vital sign measurements and oxygen use will be listed.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

13.7.5 Spirometry

Forced Vital Capacity (FVC) measurements will be summarized descriptively by treatment group and total active treatment at baseline and each scheduled visit.

FVC measurements will be listed.

13.7.6 Subjective Opiate Withdrawal Scale (SOWS)

SOWS score will be summarized descriptively by post-treatment days (post-treatment day 1,2,…,14) and treatment group and overall. Maximal SOWS score category (≤ 10, 11-20, 21-30, or > 30) by time off drug (0-1, 2, 3, 4, 5, 6, 7, or ≥ 8 days) will be summarized using frequency counts and percentages by treatment group and total active treatment. SOWS scores will be listed.

13.7.7 Physical Examinations

All physical examination data will be listed.

13.7.8 Electrocardiograms

Electrocardiogram data (e.g., heart rate, PR, QTcF intervals) will be listed. Change from baseline in HR, PR, and QTcF at each scheduled visit will be summarized. An ECG outlier table will summarize QTcF intervals out of defined ranges (including change from baseline by >30 ms or >60 ms).

13.8 Other Assessments or Analyses

Additional exploratory analyses may be undertaken of the primary and 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.
- Analysis of the proportion of subjects meeting minimal clinically important differences for patient-reported outcomes measures based on analyses of the patient-reported outcomes measures from this study and supportive qualitative studies.
- Sensitivity analyses in which patients are grouped in the dose group according to the daily dose they achieved at the start of the stable dose period.
- Analyses using different baseline definitions.
- Analyses of onset of activity.
- LCQ responder analyses using a range of responder definitions (E.g. 2.7, 3.3. and 4.1 point responder definitions)
- Each of the individual EXACT items (items 1-14), sub-domains (RS-Breathlessness, IPF-Chest, IPF-Cough, IPF-Sputum) and the Total 14 item EXACT score based on the methodology for the EXACT questionnaire.
- Daily E-RS:IPF subdomain scores and individual item scores
- AE and discontinuation summaries including timing of AEs and discontinuations.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

14.0 References

Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-343. doi:10.1136/thorax.58.4.339

EXACT-PRO Initiative The exacerbations of chronic pulmonary disease tool (exact) patient-reported outcome (pro) user manual (version 7.0) Oct. 2014. [Accessed February 25, 2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185444.pdf.

Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE Jr, Collard HR. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012 May 15;156(10):684-91. doi: 10.7326/0003-4819-156-10-201205150-00004. PMID: 22586007.

Swigris JJ, Andrae DA, Churney T, Johnson N, Scholand MB, White ES, Matsui A, Raimundo K, Evans CJ. Development and Initial Validation Analyses of the Living with Idiopathic Pulmonary Fibrosis Questionnaire. Am J Respir Crit Care Med. 2020 Dec 15;202(12):1689-1697. doi: 10.1164/rccm.202002-0415OC. PMID: 32634038; PMCID: PMC7737580.

Scoring Guide for the Living with Idiopathic Pulmonary Fibrosis (L-IPF) Questionnaire V. Trevi 12 April 2024

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

15.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
ANCOVA	Analysis of Covariance
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical and Therapeutic Class
BMI	Body Mass Index
BQL	Below Quantifiable Limit
CGI-C	Clinicians Global Impression of Change
CGI-S	Clinicians Global Impression of Severity
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CP	Conditional Power
CRF	Case Report Form
CS-NRS	Cough Severity Numerical Rating Scale
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ER-S	Evaluating Respiratory Symptoms
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire
EXACT	EXAcerbation of Chronic pulmonary disease Tool
FVC	Forced Vital Capacity
GAP	Gender, Age, and 2 Lung Physiology Variables (FVC and DLCO).
INR	International Normalized Ratio
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IRT	Interactive Response Technology
ITT	Intent-to-Treat
K	Potassium
LCQ	Leicester Cough Questionnaire
L-IPF	Living with Pulmonary Fibrosis Questionnaire
LLOQ	Lower Limit Of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Glossary of Abbreviations:

mITT	Modified intent-to-treat
Na	Sodium
NAL ER	Nalbuphine Extended-Release Tablets
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PO4	Phosphate
PK	Pharmacokinetic
PP	Per Protocol
PSO	Predictivv Study Operations
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Standard International
SpO2	Saturation of Hemoglobin with Oxygen
SOC	System Organ Class
SOWS	Subjective Opiate Withdrawal Scale
SSRE	Sample Size Re-Estimation
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
WOCBP	Women of Childbearing Potential
VAS	Visual Analogue Scale
WHO	World Health Organization

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.0 Appendices

16.1 Major Protocol Deviations Excluding Subjects from the Per Protocol Population

The following important protocol deviations and discontinuation of study drug prior to Week 6 will exclude patients from the Per Protocol Analysis. Additional important deviations may be identified by the Sponsor that warrant exclusion from this analysis prior to database lock.

Deviation Type	Deviation Sub-Type	Deviation Description	Additional Stipulation	Rationale
Procedures/ Tests	VitaloJAK related procedure not per protocol	VitaloJAK (cough monitor) not applied or removed before 20 h of recording. VitaloJAK lost or not returned	Apply PP exclusion if PD(i.e. recording time is less than 20 hours) occurred during the Baseline, Week 6 assessment, or the early termination assessment (based on post-QC cough duration)	Significantly affects interpretability of primary endpoint
Procedures/ Tests	Tests Missing questionnaires/scales/ PROs	EXACT: missing entries for 3 or more days.	Apply PP exclusion if 3 or more days of entries for Q2 of the EXACT Questionnaire for Baseline, Week 6 or for ET were missed.	Significantly affects interpretability of key secondary endpoint
CCMEDS	Prohibited meds taken during treatment and FU		Non-study opioid medication (other than loperamide) or opioid antagonist taken within 7 days prior to or on the day of cough recording at Baseline or Week 6.	Significantly affects interpretability of primary endpoint
CCMEDS	Prohibited meds taken during treatment and FU		Non-study opioid medication (other than loperamide) or opioid antagonist taken within 7 days prior to the first day of the Baseline, Week 6, or ET entries or on any days used for the calculation of these timepoints for the EXACT Questionnaire Q2	Significantly affects interpretability of key secondary endpoint
CCMEDS	Prohibited meds taken during treatment and FU		Corticosteroids for cough (prednisone daily equivalent of 5 mg or more) taken within 14 days prior to	Significantly affects interpretability of primary endpoint

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Deviation Type	Deviation Sub-Type	Deviation Description	Additional Stipulation	Rationale
			or on the day of cough recording at Baseline or Week 6.	
CCMEDS	Prohibited meds taken during treatment and FU		Corticosteroids for cough (prednisone daily equivalent of 5 mg or more) taken within 14 days prior to the first day of the Baseline, Week 6, or ET entries or on any days used for the calculation of these timepoints for the EXACT Questionnaire Q2	Significantly affects interpretability of key secondary endpoint
CCMEDS	Prohibited meds taken during treatment and FU		Initiation of antifibrotic treatment during Screening or at any time prior to Week 6	Significantly affects interpretability of primary and key secondary endpoints
Eligibility Deviations	Deviations in Incl./Excl. Criteria		Failed to meet one or more key eligibility criteria: IC#1 (IPF), IC#2 (cough severity), IC#3 (cough chronicity), EC #16 (opiates), EC #19 (steroids), or EC #23 (antifibrotics)	Significantly affects interpretability of primary and key secondary endpoints
Study Drug	Subject non-compliance / missed doses		Compliance < 80% during the fixed treatment period or >1 missed dose during the 7 days prior to the Week 6 cough recording or during the cough recording	Significantly affects interpretability of primary endpoint
Study Drug	Subject non-compliance / missed doses		Compliance < 80% during the fixed treatment period or >1 missed dose during the days of entries used for the Week 6 EXACT Questionnaire Q2 or the 7 days prior to Week 6	Significantly affects interpretability of key secondary endpoint
Study Drug	Subject non-compliance / missed doses		Discontinuation of study drug prior to Week 6*	Significantly affects interpretability of

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Deviation Type	Deviation Sub-Type	Deviation Description	Additional Stipulation	Rationale
				primary and key secondary endpoints

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.2 GAP Index and staging system

	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age, y	
	≤60	0
	61–65	1
	>65	2
P	Physiology	
	FVC, *% predicted*	
	>75	0
	50–75	1
	<50	2
	DLCO, *% predicted*	
	>55	0
	36–55	1
	≤35	2
	Cannot perform	3
	Total Possible Points	8

Stage	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-y	5.6	16.2	39.2
2-y	10.9	29.9	62.1
3-y	16.3	42.1	76.8

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.3 EQ-5D-5L

MOBILITY
I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

SELF-CARE
I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)
I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

PAIN / DISCOMFORT
I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

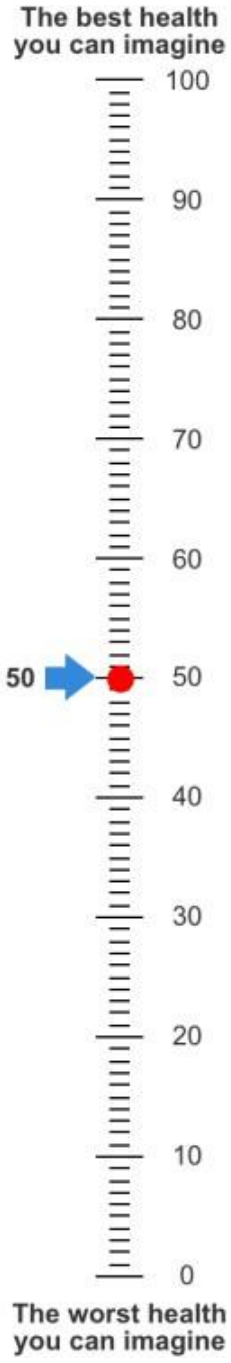
ANXIETY / DEPRESSION
I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

- We would like to know how good or bad your health is TODAY.
- You will see a scale numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please indicate on the scale how your health is TODAY.

YOUR HEALTH TODAY = **50**



Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.4 EXACT

Description	Required Text	Translation
Title	EXACT Daily Diary	EXACT Daily Diary
DD	Daily Diary	Daily Diary
Q 1 of 14	Question 1 {1} of 14	Question 1 {1} of 14
Instructions	As you answer the following questions, please select the option that best describes your experience.	As you answer the following questions, please select the option that best describes your experience.
1		
	Did your chest feel congested today?	Did your chest feel congested today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
2		
	How often did you cough today?	How often did you cough today?
	Not at all	Not at all
	Rarely	Rarely
	Occasionally	Occasionally
	Frequently	Frequently
	Almost constantly	Almost constantly
3		
	How much mucus (phlegm) did you bring up when coughing today?	How much mucus (phlegm) did you bring up when coughing today?
	None at all	None at all
	A little	A little
	Some	Some
	A great deal	A great deal
	A very great deal	A very great deal

Description	Required Text	Translation
4		
	How difficult was it to bring up mucus (phlegm) today?	How difficult was it to bring up mucus (phlegm) today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Quite a bit	Quite a bit
	Extremely	Extremely
5		
	Did you have chest discomfort today?	Did you have chest discomfort today?
	Not at all	Not at all
	Slight	Slight
	Moderate	Moderate
	Severe	Severe
	Extreme	Extreme
6		
	Did your chest feel tight today?	Did your chest feel tight today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
7		
	Were you breathless today?	Were you breathless today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Description	Required Text	Translation
8		
	Describe how breathless you were today:	Describe how breathless you were today:
	Unaware of breathlessness	Unaware of breathlessness
	Breathless during strenuous activity	Breathless during strenuous activity
	Breathless during light activity	Breathless during light activity
	Breathless when washing or dressing	Breathless when washing or dressing
	Present when resting	Present when resting
9		
	Were you short of breath today when performing your usual personal care activities like washing or dressing?	Were you short of breath today when performing your usual personal care activities like washing or dressing?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
10		
	Were you short of breath today when performing your usual indoor activities like cleaning or household work?	Were you short of breath today when performing your usual indoor activities like cleaning or household work?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these

Description	Required Text	Translation
11		
	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
12		
	Were you tired or weak today?	Were you tired or weak today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
13		
	Last night, was your sleep disturbed?	Last night, was your sleep disturbed?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Description	Required Text	Translation
14		
	How scared or worried were you about your lung problems today?	How scared or worried were you about your lung problems today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
Copyright	EXACT© 2013, Evidera, Inc. All rights reserved.	EXACT© 2013, Evidera, Inc. All rights reserved.

16.5 LCQ

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.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.6 CS-NRS

Cough Severity Numerical Rating Scale

Please indicate the severity of cough you experienced over the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Cough										Worst Possible Cough

16.7 L-IPF© Impacts

16.7.1 Questions

ITEM NUMBER	ITEM STEM	DOMAIN
1	How much did your shortness of breath prevent you from doing things you wanted to do?	Overall Impacts
2	How much did fear of becoming too short of breath limit your physical exertion?	Overall Impacts
3	How was your stamina when you exerted physically?	Overall Impacts
4	How frustrated were you by the time it took you to complete a physical activity?	Overall Impacts
5	How frustrated were you by your need to rest during or after completing a physical activity?	Overall Impacts
6	How much did coughing embarrass you?	Overall Impacts
7	How much did coughing frustrate you?	Overall Impacts
8	How much did coughing interrupt your conversations (in person or on the phone)?	Overall Impacts
9	How frightening was your coughing to you?	Overall Impacts
10	How much was your cough a problem for you?	Overall Impacts
11	How much hassle or inconvenience has IPF caused you in your day-to-day life?	Overall Impacts
12	How much did you have to rest in the middle of doing a simple chore inside the house?	Overall Impacts
13	How much did you have to pace yourself to make it through the day?	Overall Impacts
14	How much time did it take you to get yourself ready to leave the house?	Overall Impacts
15	How much were you forced to depend on other people to do things for you?	Overall Impacts
16	How much has shortness of breath affected your quality of life?	Overall Impacts
17	How much has your cough affected your quality of life?	Overall Impacts
18	How much has our energy affected your quality of life?	Overall Impacts
19	How have you felt in terms of physical health?	Overall Impacts
20	How has your quality of life been?	Overall Impacts

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.7.2 Score Conversion Table for the Overall Impacts Domain

OVERALL IMPACTS SUM SCORES	OVERALL IMPACTS EAP SUM SCORES	SE EAP SUM SCORES	OVERALL IMPACTS EAP SUM T-SCORES	SE EAP SUM T-SCORES
0	-2.35	0.50	26	4.97
1	-2.00	0.47	30	4.68
2	-1.76	0.45	32	4.53
3	-1.58	0.45	34	4.47
4	-1.43	0.44	35	4.37
5	-1.31	0.43	36	4.29
6	-1.20	0.43	38	4.25
7	-1.10	0.42	38	4.25
8	-1.02	0.43	39	4.25
9	-0.93	0.43	40	4.26
10	-0.86	0.43	41	4.28
11	-0.78	0.43	42	4.31
12	-0.71	0.43	42	4.33
13	-0.64	0.44	43	4.36
14	-0.58	0.44	44	4.39
15	-0.52	0.44	44	4.40
16	-0.46	0.44	45	4.41
17	-0.40	0.44	45	4.42
18	-0.35	0.44	46	4.43
19	-0.30	0.44	47	4.44
20	-0.25	0.45	47	4.46
21	-0.20	0.45	48	4.49
22	-0.15	0.45	48	4.51
23	-0.11	0.45	48	4.55
24	-0.07	0.46	49	4.58
25	-0.02	0.46	49	4.60
26	0.03	0.46	50	4.61
27	0.08	0.46	50	4.61
28	0.13	0.46	51	4.60
29	0.18	0.46	51	4.58
30	0.23	0.46	52	4.57
31	0.28	0.45	52	4.55
32	0.32	0.45	53	4.53
33	0.37	0.45	53	4.52
34	0.41	0.45	54	4.51
35	0.45	0.45	54	4.50
36	0.49	0.45	54	4.49
37	0.53	0.45	55	4.47
38	0.58	0.45	55	4.46
39	0.64	0.45	56	4.47
40	0.69	0.45	56	4.48
41	0.75	0.45	57	4.48
42	0.81	0.45	58	4.48
43	0.87	0.45	58	4.49
44	0.92	0.45	59	4.52
45	0.98	0.46	59	4.58
46	1.04	0.46	60	4.62
47	1.09	0.46	60	4.60
48	1.15	0.46	61	4.59
49	1.21	0.46	62	4.62
50	1.27	0.46	62	4.64
51	1.34	0.46	63	4.65
52	1.40	0.46	64	4.64
53	1.47	0.46	64	4.63
54	1.56	0.47	65	4.66
55	1.65	0.47	66	4.71
56	1.76	0.47	67	4.72
57	1.88	0.47	68	4.68
58	2.02	0.47	70	4.68
59	2.22	0.48	72	4.77
60	2.55	0.52	75	5.15

Note. The EAP sum scores were derived from a testlet model, with a general factor for all 20-items, testlet 1 (items: 1,2,4,5,11,14,15), testlet 2 (items: 6,7,8,9,10), and testlet 3 (items: 16,17,18). Omega for the fitted model is 0.97, while the marginal reliability for the general factor is = 0.81. Results were generated on Apr 15, 2022, 1:44:18 PM 2022.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.8 L-IPF© Symptoms

16.8.1 Questions

ITEM NUMBER	ITEM STEM	DOMAINS
1	Did you walk up one flight of stairs in the last 24-hours?	Overall Symptoms & Dyspnea
2	Over the last 24 hours, how short of breath have you been while sitting down, relaxing, reading, or watching TV?	Overall Symptoms & Dyspnea
3	Did you perform a grooming activity (e.g., brush teeth, shave, fix hair) in the last 24 hours?	Overall Symptoms & Dyspnea
4	Did you walk outside on a level surface in the last 24 hours?	Overall Symptoms & Dyspnea
5	Did you bathe or shower in the last 24 hours?	Overall Symptoms & Dyspnea
6	Did you lift and carry a light load (e.g., less than 10 lbs) a short distance (e.g., from one room to another) in the last 24 hours?	Overall Symptoms & Dyspnea
7	Did you become short of breath in the last 24 hours?	Overall Symptoms & Dyspnea
8	Over the last 24 hours, how often did you cough?	Overall Symptoms & Cough
9	Over the last 24 hours, how often did you cough when you took a deep breath?	Overall Symptoms & Cough
10	Over the last 24 hours, how often did you cough when you exerted yourself?	Overall Symptoms & Cough
11	Over the last 24 hours, how often did you feel an annoying tickle in your throat?	Overall Symptoms & Cough
12	Over the last 24 hours, how much did coughing have a negative effect on your energy?	Overall Symptoms & Cough
13	Over the last 24 hours, how was your energy level?	Overall Symptoms & Energy
14	Over the last 24 hours, of all that you wanted to get done, how much did you actually get done?	Overall Symptoms & Energy
15	Over the last 24 hours, how much energy did you have to do all the things you like to do?	Overall Symptoms & Energy

Note: The 5 additional questions about supplemental oxygen use are not scored and are for descriptive purposes only.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Finally, we would like to ask you 5 questions about your supplemental oxygen use.

Oxygen Question 1. Do you ever use supplemental oxygen?
(Place an "X" in one box)

- Yes →→ proceed to Oxygen Question 2.
- No →→ You have finished. Skip Oxygen Questions 2-5

Oxygen Question 2. I use supplemental oxygen...
(Place an "X" in one box)

- A →→ **only when I sleep (answer Oxygen Question 3)**
- B →→ only when I perform a physical activity (such as exercising, walking or shopping) (answer Oxygen Question 4)
- C →→ **when I sleep or perform a physical activity (such as exercising, walking or shopping, but not at rest; answer Oxygen Questions 3 and 4)**
- D →→ all the time (answer Oxygen Questions 3-5)

Oxygen Question 3. When I sleep, I most often use an oxygen flow rate of ____L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Oxygen Question 4. When I perform a physical activity (such as exercising, walking or shopping), I most often use an oxygen flow rate of ____L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Oxygen Question 5. At rest, I most often use an oxygen flow rate of ____L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.8.2 Score Conversion Table for the Dyspnea Domain

DYSPNEA SUM SCORES	DYSPNEA EAP SUM SCORES	SE EAP SUM SCORES	DYSPNEA EAP SUM T-SCORES	SE EAP SUM T-SCORES
0	-1.66	0.53	33	5.33
1	-1.16	0.41	38	4.10
2	-0.79	0.35	42	3.48
3	-0.51	0.31	44	3.15
4	-0.28	0.29	47	2.94
5	-0.07	0.28	49	2.80
6	0.12	0.27	51	2.65
7	0.29	0.25	52	2.54
8	0.45	0.25	54	2.46
9	0.60	0.24	55	2.43
10	0.74	0.24	57	2.42
11	0.88	0.24	58	2.44
12	1.03	0.25	60	2.48
13	1.18	0.25	61	2.54
14	1.33	0.26	63	2.60
15	1.48	0.27	64	2.68
16	1.65	0.28	66	2.79
17	1.82	0.29	68	2.92
18	2.02	0.31	70	3.13
19	2.24	0.34	72	3.39
20	2.50	0.37	74	3.66
21	2.83	0.39	78	3.88

Note. The EAP sum scores were derived from a single-factor model from the 15-item version of the measure (Dyspnea domain derived from items: 1-6, 15). SE = Standard error. Marginal reliability for the general factor is = 0.90. Results were generated on Apr 14, 2022, 5:09:26 PM.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.8.3 Score Conversion Table for the Cough Domain

COUGH SUM SCORES	COUGH EAP SUM SCORES	SE EAP SUM SCORES	COUGH EAP SUM T-SCORES	SE EAP SUM T-SCORES
0	-1.62	0.57	33	5.71
1	-1.05	0.46	39	4.55
2	-0.73	0.42	42	4.18
3	-0.48	0.39	45	3.91
4	-0.26	0.37	47	3.65
5	-0.05	0.34	49	3.43
6	0.14	0.33	51	3.27
7	0.31	0.32	53	3.16
8	0.48	0.31	54	3.13
9	0.65	0.31	56	3.14
10	0.82	0.32	58	3.18
11	1.01	0.33	60	3.25
12	1.22	0.35	62	3.47
13	1.44	0.37	64	3.69
14	1.71	0.40	67	4.03
15	2.09	0.49	70	4.91

Note. The EAP sum scores were derived from a single-factor model from the 15-item version of the measure (Cough domain derived from items: 7-10, 14). SE = Standard error. Marginal reliability for the general factor is = 0.86. Results were generated on Apr 14, 2022, 5:16:26 PM.

16.8.4 Score Conversion Table for the Energy Domain

ENERGY SUM SCORES	ENERGY EAP SUM SCORES	SE EAP SUM SCORES	ENERGY EAP SUM T-SCORES	SE EAP SUM T-SCORES
0	-1.62	0.51	33	5.13
1	-1.10	0.43	39	4.34
2	-0.61	0.38	43	3.84
3	-0.32	0.36	46	3.58
4	0.03	0.41	50	4.10
5	0.40	0.38	53	3.75
6	0.68	0.37	56	3.71
7	1.08	0.43	60	4.35
8	1.54	0.41	65	4.08
9	1.98	0.52	69	5.21

Note. The EAP sum scores were derived from a single-factor model from the 15-item version of the measure (Energy domain derived from items: 11-13). SE = Standard error. Marginal reliability for the general factor is = 0.80. Results were generated on Apr 14, 2022, 5:23:26 PM.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.8.5 Score Conversion Table for the Symptoms Domain

OVERALL SYMPTOMS SUM SCORES	OVERALL SYMPTOMS EAP SUM SCORES	SE EAP SUM SCORES	OVERALL SYMPTOMS EAP SUM T-SCORES	SE EAP SUM T-SCORES
0	-1.98	0.65	30	6.53
1	-1.68	0.64	33	6.40
2	-1.46	0.61	35	6.09
3	-1.28	0.59	37	5.91
4	-1.12	0.58	38	5.79
5	-0.98	0.57	40	5.73
6	-0.85	0.57	41	5.69
7	-0.73	0.56	42	5.65
8	-0.63	0.56	43	5.62
9	-0.53	0.56	44	5.61
10	-0.44	0.56	45	5.61
11	-0.35	0.56	46	5.60
12	-0.26	0.56	47	5.57
13	-0.17	0.55	48	5.54
14	-0.09	0.55	49	5.51
15	-0.02	0.55	49	5.51
16	0.05	0.55	50	5.53
17	0.12	0.56	51	5.57
18	0.19	0.56	51	5.59
19	0.26	0.56	52	5.59
20	0.32	0.56	53	5.57
21	0.39	0.55	53	5.55
22	0.46	0.55	54	5.55
23	0.53	0.56	55	5.58
24	0.59	0.56	55	5.62
25	0.66	0.57	56	5.67
26	0.73	0.57	57	5.70
27	0.79	0.57	57	5.72
28	0.86	0.57	58	5.72
29	0.92	0.57	59	5.70
30	0.99	0.57	59	5.67
31	1.06	0.56	60	5.64
32	1.14	0.56	61	5.60
33	1.21	0.56	62	5.57
34	1.29	0.56	62	5.59
35	1.36	0.56	63	5.62
36	1.44	0.56	64	5.62
37	1.52	0.56	65	5.60
38	1.61	0.56	66	5.58
39	1.71	0.56	67	5.62
40	1.82	0.57	68	5.73
41	1.96	0.58	69	5.82
42	2.10	0.58	70	5.81
43	2.23	0.58	72	5.81
44	2.40	0.60	74	5.96
45	2.64	0.62	76	6.17

Note. The EAP sum scores were derived from a testlet model, with a general factor for all 15-items, testlet 1 (items: 1-6, 15), testlet 2 (items: 7-10, 14), and testlet 3 (items: 11-13). Omega for the fitted model is 0.95, while the marginal reliability for the general factor is = 0.67. SE = Standard error. Results were generated on Apr 14, 2022, 4:55:53 PM.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.9 PGI-S Cough; PGI-S IPF; PGI-C Cough; PGI-C IPF; CGI-C Cough and CGI-S 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 IPF Symptom Severity (PGI-S IPF)

How would you rate your symptoms of idiopathic pulmonary fibrosis (IPF) over the past 7 days?

☐ No symptoms ☐ 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

Patient Global Impression of Change in IPF Symptoms (PGI-C IPF)

Compared to when you started the study, how would you rate your symptoms of idiopathic pulmonary fibrosis (IPF) over the past 7 days?

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

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

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

How would you rate the subject's cough?

☐ No cough ☐ Mild ☐ Moderate ☐ Severe

Clinical Global Impression of Change (CGI-C-Cough)

Rate the overall change in cough for the patient whether or not in your judgment it is due entirely to drug treatment. Compared to the start of the study, how much has the patient's cough changed?

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

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.10 SOWS

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.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.11 Conditional Power Based Sample Size Re-Estimation and Primary Endpoint Analysis

When approximately $[4 \times 14 = 56]/[4 \times 28 = 112]$ $(= 50\%)$ of the planned total number of subjects have completed the Week 6 measurements, an interim analysis of the primary endpoint will be performed for the purposes of sample size re-estimation (SSRE).

The SSRE will be based upon the conditional power (CP) of the 108mg NAL dose versus placebo. If CP falls within the range ≥30 to <80%, sample size for the 108mg NAL dose and placebo arms will be increased arms arm to boost power subject to a maximal sample size of 70 subjects per arm. In order to maintain blinding and allow for equal information gathering on all doses, the 27 mg and 54 mg arms will also be equally increased should the SSRE result in an increase in sample size. If CP falls outside of the ≥30 to <80% range, the study will proceed with sample size unchanged.

CP at the interim will be computed as per Mehta and Pocock (2011), Eq 6, as,

$$CP(z_i) = 1 - \Phi\left(\frac{z_\alpha\sqrt{i} - z_i}{\sqrt{i(1-i)}}\right)$$

where z_i is the interim z-value for 108mg NAL versus placebo on the primary endpoint, i is the fraction of total expected information at the interim, i.e. $i = 28/56 = 0.50$, z_α in the z-value relating to the 1-sided Type I Error rate, α, and $\Phi(\circ)$ represents the standard Normal cumulative distribution function.

If CP falls within the range ≥30 to <80%, sample size may be increased from the planned $N = 28$ per arm up to a maximum of $N^* = 70$ per arm in order to boost power towards 80%. This assumes no dropouts; with allowance for 30% dropouts, the planned and maximum sample size per arm are $N = 40$ and $N^* = 100$ respectively.

To deliver a desired CP of $1 - \beta$, the planned total sample size for the 108mg dose versus placebo comparison, denoted $N_{108}(= 2N) = 56$, must be increased to $N^*_{108} = kN_{108}$, where k is given determined by the solution of,

$$z_\beta = \frac{z_\alpha\sqrt{ik} - z_i k}{\sqrt{i(k-i)}}$$

subject to the constraint that $k \leq 70/28 = 2.5$. Thus, following the SSRE, the final total sample size for the 108mg dose versus placebo comparison will be $N^*_{108} \epsilon\, [56, 140]$ assuming no dropouts (or $N^*_{108} \epsilon\, [80, 200]$ assuming 30% dropouts). Hence, the sample size for the 108mg dose versus placebo comparison post the SSRE, n^*_{108}, is such that $n^*_{108} \epsilon\, [N_{108}, N^*_{108} - N_{108}] = [28, N^* - 28]$. Consequently, the final sample size for each of the 27 mg and 54 mg arms shall be $N^* = \frac{1}{2}N^*_{108}$ and, this, $n^* = \frac{1}{2}n^*_{108}$.

At the end of the study, when all $4N^*$ subjects have either completed the Week 6 measurements or have discontinued/become lost to follow-up/otherwise ended the study early, the Cui, Hung and Wang (1999) fixed weights approach will be applied to the primary endpoint analysis avoid alpha inflation.

Denote the pre and post SSRE subjects for any given dose arm, d, as n_{id} and $N^*_d - n_{id}$ and, similarly, for placebo denote pre and post SSRE subjects as n_{ip} and $N^*_p - n_{ip}$ respectively. The z-value for the primary endpoint in these $n_{ip} + n_{id}$ subjects included in the interim SSRE calculation will be computed and denoted as z_{pre} ; and, similarly, the z-value for the primary endpoint in the remaining $N^*_p - n_{ip} + N^*_d - n_{id}$ subjects will be computed and denoted as z_{post} . Then the combined z-value for the primary endpoint for dose d compared to placebo will be given as,

$$z_{comb} = \omega_{pre} z_{pre} + \omega_{post} z_{post}$$

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

where $\omega_{pre} = \omega_{post} = \sqrt{14/28}$. The associated 1-sided p-value for dose d compared to placebo will be given as

$p_{comb} = 1 - \Phi^{-1}(z_{comb})$

In terms of treatment effect estimation, denote the treatment effect estimate for the primary endpoint in the $n_{ip} + n_{id}$ subjects included in the interim SSRE as θ_{pre} and in the $N^* - n_{ip} + N^* - n_{id}$ post interim subjects as θ_{post}. Define $\omega^*_{post} = \sqrt{(N^* + N^*)/2N}$. As per Lawrence 2003, the overall treatment effect point estimate for the primary endpoint, θ, and associated standard error, $\mathrm{SE}(\theta)$, are given by,

$$\theta = \frac{\omega^2_{pre} \cdot \theta_{pre} + \omega_{post} \cdot \sqrt{(\omega^{*2}_{post} - \omega^2_{pre})}\theta_{post}}{\omega^2_{pre} + \omega_{post} \cdot \sqrt{(\omega^{*2}_{post} - \omega^2_{pre})}}$$

$$SE(\theta) = \sqrt{\frac{4\hat{\sigma}^2}{N\,(\omega^2_{pre} + \omega_{post} \cdot \sqrt{(\omega^{*2}_{post} - \omega^2_{pre})})}}$$

Further, denote the overall LS Mean for the primary endpoint in the dose arm d as $\mathcal{L}_d$, then,

$$\mathcal{L}_d = \frac{\omega^2_{pre} \cdot \mathcal{L}_{d,pre} + \omega_{post} \cdot \sqrt{(\omega^{*2}_{post} - \omega^2_{pre})}\mathcal{L}_{d,post}}{\omega^2_1 + \omega_2 \cdot \sqrt{(\omega^{*2}_2 - \omega^2_1)}}$$

$$SE(\mathcal{L}_D) = \sqrt{\frac{2\hat{\sigma}^2}{N\,(\omega^2_{pre} + \omega_{post} \cdot \sqrt{(\omega^{*2}_{post} - \omega^2_{pre})})}}$$

And, similarly for the placebo arm. And where $\hat{\sigma}^2$ is the residual error estimated based upon the based on the intended sample size, N, per arm.

FDA co-authored publications, and supportive simulations, demonstrate that the use of fixed weights as per Cui, Hung and Wang (1999) is necessary to avoid alpha inflation associated with the SSRE procedure. For this reason, the fixed weights approach will be used in the principal analysis of the primary endpoint. In addition, a supportive analysis of the primary endpoint will also be performed using an unweighted test statistic regardless of the risk of Type I error inflation and the associated potential bias in treatment effect estimation.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.12 Analysis Windows

This section defines the analysis windows that will be utilized for various assessments performed for this study. Analysis windows will be used to associate assessments with a scheduled visit for summarizing data by visit. The study day will be used to determine the associated visit window.

The schedules of events from the protocol (Protocol Amendment 2) are shown in Table 1 Schedule of Events and Table 2 Schedule of Events (SoE) for PROs.

16.12.1 Efficacy Measures

For subjects who have discontinued treatment early, discontinuation visit procedures will be categorized according to the study day on which the procedures were completed and only included in the by visit analyses if a dose was received ≤2 days prior to the assessment. If more than one valid assessment was performed during a Visit's analysis window, by convention, the assessment closest to the target day will be used; if both assessments are equidistant from the target day, the first assessment will be used.

Analysis Windows for Cough Counts

Table 8: Analysis Windows for Cough Counts

Visit	Start Day of Window	Target Day Per Protocol	End Day of Window
Day -1	Day -7	Day -1	Prior to first dose
Week 2	Day -1, after first dose	Day 13 (-2 d)	Day 20
Week 4	Day 21	Day 28 (+/- 2d)	Day 33
Week 6	Day 34	Day 42 (+/- 2d)	Date recording ended ≤ Last dose date + 2 days*

Note 1: Cough count collection begins on the day of the clinic visit and is completed 24 hours later. The target dates is the date that the cough count collection started.
Note 2: Subjects utilizing the +1 or +2-day window at the Day 42 visit will continue on study drug until their visit.
*For subjects who did not prematurely discontinue treatment. For subjects who discontinued treatment prematurely, see general window rules above.

Analysis Windows for Patient-Reported Outcome and Clinician Impression Efficacy Measures

The EXACT questionnaire is collected daily; thus, there are no analysis windows defined for this measure. Analysis windows for the Cough Severity Numerical Rating Scale (CS-NRS), Living with Pulmonary Fibrosis Symptom Domain (L-IPF symptom), Living with Pulmonary Fibrosis Impacts Domain (L-IPF impacts), Leicester Cough Questionnaire (LCQ), Patient Global Impression – Static for Cough and IPF (PGI-S Cough and PGI-S IPF, respectively), Patient Global Impression – Change for Cough and IPF (PGI-C Cough and PGI-C IPF, respectively), Clinician's Global Impression – Static (CGI-S), Clinician's Global Impression – Change (CGI-C), and the European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L) are described below.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Table 9: Analysis Windows for CS-NRS

Visit	Target Day (questionnaire release day)	End Day of Window
Day -1	Day 1	Prior to first dose
Week 1	Day 7	Day 13
Week 2	Day 14	Day 20
Week 3	Day 21	Day 27
Week 4	Day 28	Day 34
Week 5	Day 35	Day 41
Week 6/End of Treatment	Last dose date + 1 day	Last dose date +2 days*

Note 1: eDiary questionnaires (other than the EXACT) for Days 1 – 35 are automatically released on the target study day and remain available for 6 days. eDiary questionaires for Week 6 are released 1 day after completion of the end of treatment IRT transaction by the site and remain available for 6 days. For early discontinuations of study drug, the questionnaires release upon completion of the discontinuation transaction in the IRT regardless of the clinic visit timing and remain available until the end of study for a given subject.
Note 2: Subjects utilizing the +1 or +2-day window at the Day 42 visit will continue on study drug until their visit.
Note 3: The recall period for CS-NRS is 24 hours.
* For subjects who did not prematurely discontinue treatment. For subjects who discontinued treatment prematurely, see general window rules above.

Table 10: Analysis Windows for L-IPF Impacts, L-IPF Symptoms, LCQ, and EQ-5D-5L,

Visit	Target Day (questionnaire release day)	End Day of Window
Day -1	Day 1	Prior to first dose
Week 6/End of Treatment	Last dose date +1 day	Last dose date +2 days*

Note 1: eDiary questionnaires (other than the EXACT) for Days 1 – 35 are automatically released on the target study day and remain available for 6 days. eDiary questionaires for Week 6 are released 1 day after completion of the end of treatment IRT transaction by the site and remain available for 6 days. For early discontinuations of study drug, the questionnaires release upon completion of the discontinuation transaction in the IRT regardless of the clinic visit timing and remain available until the end of study for a given subject.
Note 2: Subjects utilizing the +1 or +2-day window at the Day 42 visit will continue on study drug until their visit.
Note 3: The recall period is 7 days for L-IPF Impacts; 24-hours for L-IPF symptoms and LCQ; and “today” for the EQ-5D-5L.
*For subjects who did not prematurely discontinue treatment. For subjects who discontinued treatment prematurely, see window rules above.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Table 11: Analysis Windows for PGI-S Cough, PGI-S IPF, PGI-C Cough, PGI-C IPF, CGI-S, and CGI-C

Visit	Measure	Target Day (questionnaire release day)	End Day of Window
Day -1	PGI-S IPF PGI-S cough CGI-S	Day 1	Prior to first dose
Week 2	PGI-S IPF PGI-S cough PGI-C IPF PGI-C cough	Day 14	Day 27
Week 4	PGI-S IPF PGI-S cough PGI-C IPF PGI-C cough	Day 28	Day 41
Week 6/End of Treatment	PGI-S IPF PGI-S cough PGI-C IPF PGI-C cough CGI-S CGI-C	Last dose date +1 day	Last dose date +2 days*

Note 1: eDiary questionnaires (other than the EXACT) for Days 1 – 35 are automatically released on the target study day and remain available for 6 days. eDiary questionaires for Week 6 are released 1 day after completion of the end of treatment IRT transaction by the site and remain available for 6 days. For early discontinuations of study drug, the questionnaires release upon completion of the discontinuation transaction in the IRT regardless of the clinic visit timing and remain available until the end of study for a given subject.
Note 2: Subjects utilizing the +1 or +2-day window at the Day 42 visit will continue on study drug until their visit.
Note 3: The recall period is 7 days for all PGI measures; The CGI-C recall period is to the beginning of the study. The CGI-S does not have a specified recall period.
*For subjects who did not prematurely discontinue treatment. For subjects who discontinued treatment prematurely, see window rules above.

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

16.12.2 Safety Measures

For subjects who have discontinued treatment early, discontinuation visit procedures will be categorized according to the study day on which the procedures were completed and only included in the by visit analyses if a dose was received ≤3 days prior to the assessment. Analysis Windows for the Subjective Opiate Withdrawal Scale (SOWS), Vital Signs, ECG Measurements, clinical laboratory, and spirometry measurements are defined in this section.

Table 12: Analysis Windows for SOWS

Visit	Target Day (questionnaire release day)	End Day of Window
Day -1	Day 1	Prior to first dose
Week 1	Day 7	Day 34
Week 5	Day 35	Day 41
Week 6/End of Treatment	Last dose date + 1 day	Last dose date + 1 day
Follow-Up	Last dose date +2 days	Last dose date +2 days
	Last dose date +3 days	Last dose date +3 days
	Last dose date +4 days	Last dose date +4 days
	Last dose date +5 days	Last dose date +5 days
	Last dose date +6 days	Last dose date +6 days
	Last dose date +7 days	Last dose date +7 days
	Last dose date +8 days	Last dose date +8 days
	Last dose date +9 days	Last dose date +9 days
	Last dose date +10 days	Last dose date +10 days
	Last dose date +11 days	Last dose date +11 days
	Last dose date +12 days	Last dose date +12 days
	Last dose date +13 days	Last dose date +13 days
	Last dose date +14 days	Last dose date +14 days

Note 1: eDiary questionnaires (other than the EXACT) for Days 1 – 35 are automatically released on the target study day and remain available for 6 days. eDiary questionaires for Week 6 are released 1 day after completion of the end of treatment IRT transaction by the site and remain available for 6 days. For early discontinuations of study drug, the questionnaires release upon completion of the discontinuation transaction in the IRT regardless of the clinic visit timing and remain available until the end of study for a given subject.
Note 2: Subjects utilizing the +1 or +2-day window at the Day 42 visit will continue on study drug until their visit.
Note 3: There is no recall period for SOWS. Responses are based on the subjects' symptoms "now".

Strictly Confidential. © 2025, ICON. All rights reserved.

Docusign Envelope ID: DA82E25A-9D66-4A2E-B7B9-BE04881B8249

Table 13: Analysis Windows for Vital Signs

Visit	Start Day of Window	Target Day Per Protocol	End Day of Window
Day -1	Screening start**	Day -1	Prior to first dose
Week 2	Day -1, after first dose	Day 13 (-2 d)	Day 20
Week 4	Day 21	Day 28 (+/- 2d)	Day 33
Week 6	Day 34	Day 42 (+/- 2d)	Last dose + 3 days*
Week 8	Last dose + 3 days	Day 48 (+/- 3d)	Day 51

*For subjects who did not prematurely discontinue treatment. For subjects who discontinued treatment prematurely, see window rules above.
**When there are multiple measurements during Screening, the measurement closest to Day -1 will be used.

Table 14: Analysis Windows for Clinical Laboratory Tests, ECG, and Spirometry

Visit	Measurements	Start Day of Window	Target Day Per Protocol	End Day of Window
Day -1	Lab ECG Spirometry	Screening start**	Day -1	Prior to first dose
Week 2	Lab ECG	Day -1, after first dose	Day 13 (-2d)	Day 29
Week 6	Lab ECG Spirometry	Day 30	Day 42 (+/- 2d)	Last dose + 3 days*

*For subjects who did not prematurely discontinue treatment. For subjects who discontinued treatment prematurely, see window rules above.
**When there are multiple measurements during Screening, the measurement closest to Day -1 will be used.

Strictly Confidential. © 2025, ICON. All rights reserved.