

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: Protocol Amendment 2: 20 May 2024

CLINICAL TRIAL PROTOCOL: NAL03-202

Study 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)

Short Study Title Cough Reduction in IPF with nalbuphine ER (CORAL)

Study Number: NAL03-202

Study Phase: 2b

Product Name: Nalbuphine Extended-Release Tablets (NAL ER)

Reference Number/s: EU-CT 2023-505296-72-00

Indication: Cough in Idiopathic Pulmonary Fibrosis

Investigators: Multicenter

Sponsor: Trevi Therapeutics, Inc.
195 Church Street, 16th Floor
New Haven, CT 06510, USA

Sponsor Contact: [REDACTED]

Medical Monitor: [REDACTED], MD

Protocol Version **Protocol Amendment 2: 20-May-2024**

Amendment Scope First global protocol revision including all country-specific amendments and administrative letters, and global changes

Confidentiality Statement

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Date
<i>Protocol Amendment 2</i>	<i>20-May-2024</i>
<i>Protocol Amendment 1 (Canada)</i>	<i>15-Aug-2023</i>
<i>Protocol Amendment 0a-UK</i>	<i>11-Oct-2023</i>
<i>Protocol Amendment 0a-EU</i>	<i>06-Nov-2023</i>
<i>Administrative Letter 1 to Protocol Amendment 0a-UK</i>	<i>10-Jan-2024</i>
<i>Original Protocol</i>	<i>22-Jun-2023</i>

AMENDMENT 2: 20-MAY-2024

Overall Rationale for the Amendment: Protocol Amendment 2 was created to align local amendments into one global unified Protocol Amendment and add additional clarifications and updates. All changes are detailed below:

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
Synopsis and SoE	Align the synopsis and SoE with the body of the protocol. See the applicable section for details and rationale for the updates in the synopsis and SoE.	Administrative
List of Abbreviations	Added EOS, E-RS [®] :IPF, FU, IUS, and PP, TdP,, corrected or removed abbreviations. Terms with © or ® are marked at important points in the text, and symbols removed from the rest of the text.	Administrative
Throughout Protocol	Added text “ <i>End of Study</i> ” or “ <i>EOS</i> ” to references to the “ <i>Follow-Up</i> ” or “ <i>FU</i> ” visit	Clarify End of Study for Subject
2.2 Background Information about Nalbuphine	Added the text “ <i>when the originator product, Nubain 10 mg/ml solution for injection, was registered in the Netherlands by Bristol-Myers Squibb. In 2020, an application from Altamedics GmbH for Nubain 10 mg/ml Injektionslösung was approved in Germany, Austria, and the Netherlands for the...</i> ”	Clarify commercial availability of Nalbuphine in the EU
2.4 Rationale for Study Design	Added text “ <i>As there are currently no approved pharmacological therapies for the treatment of cough related to IPF, the use of placebo is acceptable in the current design, in accordance with the Declaration of Helsinki ethical principles for medical research.</i> ”	Clarify alternative therapies and rationale for use of placebo

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
2.5 Risk/Benefit and Ethical Assessment	Added four paragraphs starting and ending with the below text: <i>“The TR12 study demonstrated that subjects treated with doses escalating to 162 mg BID of NAL ER showed a 76.1% improvement (95% CI, –83.1 to –69.1) in the geometric mean percent change in objective cough frequency compared</i> ... <i>Analysis confirmed the lack of effect of nalbuphine on change from pre-dose in vital parameters, including respiratory parameters SpO2 and RR, and that increasing the dose from 81 mg to 486 mg did not show a dose response in the degree of change.”</i> This text replaced and expanded upon one deleted paragraph starting with <i>“The prescribing information for parenterally administered nalbuphine...”</i>	Increase detail on the risk assessment of the potential for respiratory depression
3.2 Key Secondary Objective; 3.3. Secondary Objective; and 9.9.2 Secondary Efficacy Endpoints	Clarified the nomenclature and relationship between the EXACT and the E-RS:IPF questionnaires and domains.	Correct the nomenclature
3.3 Secondary Objective	LCQ Objective - Added text <i>“total and domain scores (physical, psychological, and social domains)”</i> to allow more detailed analysis, and updated the endpoints to align.	Add domain score analyses for this instrument
3.3 Secondary Objectives	Patient and Clinical Global Assessments – Separated endpoint for assessment of change, as it is not done at baseline. Added <i>“Proportion of subjects: improvement by ≥ 1 and ≥ 2 categories...”</i>)	Add categorical analyses for these assessments, and add clarifications
3.3 Secondary Objective	L-IPF Symptoms Questionnaire – Added analysis of domains	Add domain score analyses for this instrument
4.1 Study Duration and Dates	Added text <i>“The overall end of study is defined as the last study visit for the last patient (LPLV)”</i>	Clarify EOS for the overall study
4.1 Study Duration and Dates	Added text <i>“Following their participation in the study, subjects will return to the care of their usual physician for the continued management of their condition or, if needed, they will be referred to appropriate care.”</i>	Define subject return to routine care at the end of the study
4.2 Overall Study Design	Update paragraph on instructions for subjects discontinuing study drug	Add detail for clarity
5.2 and 5.3 Inclusion and Exclusion Criteria	Inclusion #1 Deleted <i>“Principle”</i> Exclusion #2 – updated 89mL to 90mL Exclusion #6 b) – added <i>“either a”</i> and removed <i>“and”</i> Exclusion #12 – added <i>“as assessed by the investigator”</i> Exclusion #19 – added <i>“prescribed as”</i>	Added detail to correct and clarify
5.3 Exclusion Criteria	Exclusion #14 – new criteria: <i>“Known hypersensitivity to nalbuphine or to NAL ER excipients”</i> as aligned with IB section 6.4 <i>“Contraindications”</i>	Align with IB
5.3 Exclusion Criteria	Exclusion #25 – new criteria: <i>“Use of a medication having a “known risk” of Torsade de Pointes (TdP) ...”</i>	Align with IB Section 6.7

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
6.5 Multiple Missed Doses	Changed 6 missed doses (approx. 3 days) to 3 missed doses (approx. 1.5 days) as the threshold for discussion with the study Medical Monitor/s	Facilitate Medical Monitor contact at an earlier timepoint
7.2 Reporting of Adverse Events	Added text “ <i>Non-serious adverse events related to ECG, laboratory, or physical examination findings</i> ... <i>the Adverse Event eCRF.</i> ” To replace the text “ <i>Clinically significant findings noted prior to the start of investigational product treatment will be recorded as medical history</i> ”.	Add detail for clarity
7.2.2 Adverse Events Requiring Additional Narratives	Added the terms: <i>Dissociation, Feeling drunk and Hallucinations (any)</i> Revised the terms: <i>Polysubstance dependence to Substance dependence, Intentional drug misuse to Intentional product misuse</i> Removed term <i>Elevated Mood</i>	Revisions due to MedDRA updates and Sponsor Decision
7.2.4 Severity Grading	Updated section title and added the text “ <i>The AE terms that are not found in the most current version of CTCAE will be graded according to the general guideline in Table 5 CTCAE Severity Grading</i> ”.	Clarify the use of the CTCAE guidelines and the general severity grading table.
7.4 Pregnancy	Clarified procedures in case of pregnancy, and updated that the outcome of the pregnancy will be followed up no later than 6-8 weeks following estimated due date	Update for clarity
8.4 Subject Symptom and Medication Logs and 8.6 Concomitant Medication and Therapy Assessments	Added text for Symptom Log that “ <i>new and/or changed</i> ” items should be recorded. Added text for the Medication Log that the addition, change, or discontinuation of “ <i>medications, therapies, including oxygen therapy, over-the-counter (OTC) medications, herbal medications, vitamins, and nutritional supplements will be reported</i> ” Added text that the logs “ <i>reviewed by staff and applicable information entered in eCRF</i> ”	Clarify how the subject logs should be used
8.6.1 Prohibited and Restricted Medications, and Washout Including Table 7	Clarified implications of taking restricted medication for withdrawal and defined stable dose. Table 7 updated table to align with the medication exclusion criteria, and for consistency	Added detail for clarity, and update for consistency
8.11 Clinical Laboratory Tests	Added text “ <i>Once processed, samples will be stored for an interim period at the site before shipping to the location where the analysis will be performed. Samples can be stored for up to 1 month, before being destroyed at the analysis location.</i> ” “ <i>at the central lab using consistent methodology and procedures globally at the testing locations (ICON Laboratories in Ireland, US, and Singapore)</i> ” Clarified that only the Urine Pregnancy Test is tested locally at site.	Define the testing, storage time and location of routine lab samples
8.12 Blood Sampling for Pharmacokinetics (PK)	Added text “ <i>Once processed, samples will be stored for an interim period at the site, before shipping to the central lab for forwarding to the PK lab. Samples that are sent to the PK lab can be stored for up to 5 years in case of the need for retesting for this study before being destroyed.</i> ”	Define the storage time and location of PK lab samples

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
8.13 WOCBP Pregnancy test, and Contraceptive counselling	Added text “ <i>without an alternative medical or medication cause (e.g. hormonal treatments)</i> ” and “ <i>Permanently</i> ”, and expanded on definition of permanently sterile, for definition of non-WOCBP. Added text “ <i>Intrauterine hormone-releasing system (IUS)</i> ”, as acceptable method of birth control.	Align with Clinical Trials Facilitation & Coordination Group (CTFG) Guidance
8.16 24-hour Digital Cough Monitor	Added text about the measures taken to preserve privacy: “ <i>The recording is encrypted on the device and transferred electronically to the UK via a secure web portal.</i> ” And “ <i>by specially trained individuals working under strict SOPs to ensure confidentiality</i> ... <i>do not have access to listen to the records</i> ”	Add detail for clarity
8.17 Patient Reported Outcome (PRO) Questionnaires	Clarified that the contents of the EXACT includes the E-RS:IPF respiratory symptom subscales. Clarified that PROs will be completed the date after the planned visit date. This correction was also implemented in the SoE for PROs, footnote 2.	Add detail for clarity
8.17.1 SOWS (Subjective Opiate Withdrawal Scale)	Added text “ <i>Subject reported symptoms of withdrawal captured on the SOWS will not be reported as an Adverse Event unless reported verbally as part of the overall AE assessment at each visit</i> ”, to replace text requiring reporting of SOWS answers as Medical History or Adverse Events.	Correct the documentation of SOWS PRO answers
8.22 Tolerance and Titration Symptoms Management	Added text about consultation with the medical monitor in case of missed doses or continued lack of tolerance.	Increase medical monitor contact
8.23 Premature Discontinuation	Clarified the protocol allowed reasons for discontinuation from the study. Added text “ <i>Subjects have the right to discontinue</i> ... <i>discontinuation has occurred.</i> ” Clarified the steps to be taken if a subject permanently discontinues the study drug. Added the text that “ <i>the last study procedure or visit under the subject’s consent will be considered End of Study</i> ”	Facilitate Medical Monitor real-time awareness of premature discontinuations Add detail for clarity
8.24 Appropriateness of measures	Added text “ <i>24-hour cough recordings are currently recognized as the standard measure of efficacy in cough studies.</i> ” “ <i>PROs will be performed on an electronic device (e-diary) with a CE Mark for EU.</i> ”	Clarify the assessments and devices selected for the study measures
9.2 Intercurrent Event Handling	Section rewritten to reflect the updates in the SAP about the handling of missing data, dropouts, and subjects with changes to dosing regimen	Clarify the planned handling of intercurrent events

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
9.5 Analysis Populations	Added text “ <i>Per Protocol (PP) population: The PP population will consist of all subjects in the mITT population who have a treatment compliance >80% during the fixed dose period and do not have a protocol deviation that excludes subjects from the PP population. A complete list of protocol deviations that will exclude subjects from the PP population will be provided in the SAP. Subjects who are withdrawn from the study by the sponsor due to a deviation (see Section 10.9) will be excluded from the PP population</i> ”	Increase detail on the per protocol population
9.9 Efficacy Analyses	Updated the Efficacy Analyses with text “ <i>The primary efficacy analysis will be a mixed model repeated measures (MMRM)</i> ... <i>will also be included as covariates.</i> ” And “ <i>The key secondary efficacy analysis will be an MMRM of relative change from baseline</i> ... <i>Missing data rules will be specified in the statistical analysis plan.</i> ” And “ <i>All analyses of the EXACT questionnaire</i> ... <i>for which the EXACT was designed.</i> ”	Summarize the planned analyses accurately, aligned with the SAP
9.12 Other Assessment or Analysis	Section rewritten to summarize the additional complexity added in the SAP:	Summarize the planned analyses accurately, aligned with SAP
10.1 Quality Control and Assurance	Added the term “will” instead of “should” for ensuring adequate qualifications of study team. Information about protocol deviations in section 10.1 was incorporated into section 10.9, and removed from this section, to avoid duplication.	Make investigator responsibility compulsory
10.6 Patient Confidentiality and Data Protection	Added text to this section: “(e.g., from the e-diary, cough monitor, labs)” “(pseudonymized)” “ <i>This code list will remain on site and kept in a secure manner with the study documentation, with access limited to authorized individuals.</i> ” “ <i>Identifiable (non- pseudonymized) personal study-related data will be accessed by the sponsor</i> ... <i>used in this way to participate in the study.</i> ” “ <i>The compliance with these requirements is confirmed and documented throughout</i> ... <i>data transfer agreements and quality agreements, where appropriate.</i> ” “ <i>In case of security breach procedures for reporting and disclosure within the regulations and timelines of the applicable countries for the study will be followed.</i> ” The above text replaced and expanded upon the below deleted text:	Increase detail on the data protection processes

SECTION # AND NAME	DESCRIPTION OF CHANGE	BRIEF RATIONALE
	<i>“The level of disclosure will be explained to the subject who will be required to give consent for their data to be used as described in the informed consent”</i>	
10.9 Protocol Violations/ Deviations	Replace “non evaluable” with “ineligible for inclusion in the Per Protocol population.”	Clarify the term non-evaluable
10.11 Data Generation and Analysis	Added text “ <i>The data generated to answer the objectives of the study are:</i> ... <i>and no data is recorded in the eCRF directly. Data will be</i> ” And “ <i>The following data is generated by the subject or by a vendor,</i> ... <i>source of the actions and results themselves will be the vendor database.</i> ”	Clarify data collected, and the location of the source data
10.12 Retention of Data	Replaced text “as long as needed” with “25 years” Deleted “and sponsor requirements” and added “before destroying the data”	Clarify data retention time and destruction
10.14 Publication and Disclosure Policy	Added text “ <i>The results of the study will be posted to the publicly accessible website ClinicalTrials.gov independent of the outcome of the study.</i> ”	Clarify disclosure of results
11 References and throughout	Added new references, and removed references no longer applicable. Corrected, added, or aligned in-text references throughout where required.	Administrative

1 PROTOCOL SYNOPSIS

1.1 Synopsis

Name of Sponsor/Company: Trevi Therapeutics, Inc.		Study Number: NAL03-202	Protocol Amendment 2
Name of Finished Product: Nalbuphine Extended-Release Tablets (NAL ER)			
Name of Active Ingredient: nalbuphine hydrochloride (HCl)			
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel, 4-Arm Dose Ranging Study of the Safety and Efficacy of NAL ER Tablets for the Treatment of Cough in Idiopathic Pulmonary Fibrosis (IPF)			
Short Study Title: Cough Reduction in IPF with nalbuphine ER (CORAL)			
Study Phase: Phase 2b	Study Centers: Approximately 75 centers		Protocol Amendment 2 20-May-2024
Planned Study Period: 2023 to 2024	Duration of Treatment per subject: 6 Weeks	Duration of Study per subject: up to 12 Weeks	
Number of Subjects: Approximately 160 subjects with diagnosed IPF will be randomized. The number of subjects may be adjusted up to a maximum of approximately 400 based on a Sample Size Re-Estimation (SSRE).			
Study Objectives and Efficacy Endpoints:			
Objective		Endpoint	
Primary Objective			
Effect of NAL ER on 24-hour cough frequency (coughs per hour) at Week 6 using objective digital cough monitoring.	Relative change from Baseline in 24-hour cough frequency (coughs per hour) at Week 6 for NAL ER compared with placebo.		
Key Secondary Objective			
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) Week 6.	Relative change from Baseline in the E-RS:IPF Cough subscale at Week 6 for NAL ER compared with placebo.		

Secondary Objectives	
Safety and tolerability of NAL ER in the study population.	- Adverse events, clinical laboratory assessments, vital signs, spirometry and physical examination summaries. - Electrocardiogram (ECG) summaries [ECGs will be analyzed in a separate report]. - Subjective Opiate Withdrawal Scale (SOWS) daily summaries for the 14 days following the last dose of investigational product.
24-hour cough frequency (Coughs per hour).	- Relative change from Baseline in 24-hour cough frequency (coughs per hour) at Week 2, 4 and 6 for NAL ER compared with placebo. - Proportion of responders with $\geq 30\%$, $\geq 50\%$ and $\geq 75\%$ 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 (Evaluating Respiratory Symptoms in Idiopathic Pulmonary Fibrosis) and subscales as collected in the EXACT [®] (EXacerbation of Chronic pulmonary disease Tool)	- Change from Baseline in the E-RS: IPF Cough subscale at Week 1, 2, 3, 4, 5, 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. - 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)	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 and domain scores (physical, psychological, and social domains)	- Change from Baseline in the LCQ total scores 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 [®] (Living with Pulmonary Fibrosis Impacts Questionnaire)	Change from Baseline in the L-IPF at Week 6, for NAL ER compared with placebo.
L-IPF [®] (Living with Pulmonary Fibrosis Symptoms Questionnaire)	Change from Baseline in the L-IPF and its domains at Week 6, for NAL ER compared with placebo.
EQ-5D-5L [™]	Change from Baseline in the EQ-5D-5L at Week 6, for NAL ER compared with placebo.
PGI-S Cough; PGI-C Cough	Change from Baseline in the PGI-S Cough at Week 2, 4, and 6, for NAL ER compared with placebo.

Name of Sponsor/Company: Trevi Therapeutics, Inc.	Study Number: NAL03-202	Protocol Amendment 2
(Patient Global Impression of Severity and Change for Cough)	- 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 post-baseline 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 post-baseline timepoint for NAL ER compared with placebo.	
CGI-S, CGI-C (Clinical Global Impression of Severity and 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.	
Pharmacokinetics: Nalbuphine (and/or metabolites) plasma concentration will be measured for each treatment group at all visits where subject is on drug. A PK sample will be drawn and correlated with the time of IP intake as reported by the subject.		
Study Design: This is a multi-center randomized, double-blind, placebo-controlled, parallel, 4-arm study. After meeting eligibility during the Screening Period, subjects will be randomized (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 Table: Dosing Scheme, 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: Study Schematic, and Section 1.2 Schedule of Events, Table 1 and Table 2. If permanent discontinuation of investigational product occurs the discontinuation and safety follow-up/EOS visits should be performed. The subject will then be contacted at the calculated timepoint of Week 6 (42 days post baseline) by phone to collect information on serious adverse events (SAEs) and vital status. An independent Data Safety Monitoring Board (DSMB) will periodically review selected data.		

Name of Sponsor/Company: Trevi Therapeutics, Inc.	Study Number: NAL03-202	Protocol Amendment 2
---	-----------------------------------	-----------------------------

Figure: Study Schematic

Screening Period	Titration Period	Fixed dose period	Washout Period
		NAL ER 108 mg Tablets BID	
		NAL ER 54 mg Tablets BID	
		NAL ER 27 mg Tablets BID	
		Placebo Tablets BID	
Day -1 1:1:1:1 Randomization or Screen Failure		Week 6 Primary End Point	
Week -4 Day -1	Week 1 Week 2	Week 3 Week 4 Week 5	Week 6 Week 8

Table: Dosing Scheme

Study Day / Week	NAL ER 27 mg BID		NAL ER 54 mg BID		NAL ER 108 mg BID		Placebo Arm	
	AM	PM	AM	PM	AM	PM	AM	PM
1	-	27	-	27	-	27	-	Placebo
2	-	27	-	27	-	27	-	Placebo
3	27	27	27	27	27	27	Placebo	Placebo
4	27	27	27	27	27	27	Placebo	Placebo
5	27	27	27	27	27	27	Placebo	Placebo
6	27	27	27	27	27	27	Placebo	Placebo
7	27	27	27	54	27	54	Placebo	Placebo
8	27	27	54	54	54	54	Placebo	Placebo
9	27	27	54	54	54	54	Placebo	Placebo
10	27	27	54	54	54	54	Placebo	Placebo
11	27	27	54	54	54	54	Placebo	Placebo
12	27	27	54	54	54	54	Placebo	Placebo
13	27	27	54	54	54	54	Placebo	Placebo
14	27	27	54	54	54	108	Placebo	Placebo
Week 3- Week 6	27	27	54	54	108	108	Placebo	Placebo

Name of Sponsor/Company: Trevi Therapeutics, Inc.	Study Number: NAL03-202	Protocol Amendment 2
Study Population: <u>Inclusion Criteria</u> Subjects eligible for randomization to receive investigational product must meet all the following criteria: 1. Diagnosis of IPF as determined by the Investigator based on ATS/ERS/JRS/ALAT guidelines (<i>Raghu et al, 2018; updated in Raghu et al, 2022</i>). 2. Cough Severity Score ≥ 4 on CS-NRS (Cough Severity Numerical Rating Scale) during the Screening period and Baseline. 3. History of chronic cough for at least 8 weeks before screening. 4. SpO₂ $\geq 92\%$, taken after at least 5 minutes in a sitting position, undisturbed and non-stimulated (Saturation of Hemoglobin with Oxygen as Measured by Pulse Oximetry). 5. FVC $\geq 40\%$ predicted of normal - Forced Vital Capacity, as determined by spirometry adhering to ATS/ERS guidelines (<i>Graham et al, 2019</i>). 6. DLCO $\geq 25\%$ predicted of normal - Diffusing capacity of the lungs for carbon monoxide corrected for hemoglobin, assessed within the last 12 weeks, or at the time of screening. 7. Males or females ages 18 years and older at the time of consent. 8. Willing and able to provide written informed consent, comply with study requirements and restrictions, and agree to the confidential use and storage of all data and use of all anonymized data for publication including scientific publication.		
<u>Exclusion Criteria</u> Subjects meeting any of the following criteria are not eligible for participation in the study: 1. Currently on continuous oxygen therapy for longer than 16 hours at any level or delivered by any modality. Intermittent oxygen use of any duration over any given 24-hour period is allowed. 2. Inadequate swallow reflex as assessed by the ability to sip 3 fluid oz (or 90 mL) of water without coughing or choking. 3. Upper or lower respiratory tract infection in the last 8 weeks prior to the baseline visit. 4. Clinical history of aspiration pneumonitis. 5. Diagnosis of sleep apnea. 6. Cardiac Safety: Mean QTcF value of 3 centrally read screening electrocardiograms (ECGs) calculated as a) $\geq 470\text{ms}$ if QRS $< 120\text{ms}$ or b) $\geq 500\text{ms}$ in the presence of either a Right Bundle Branch Block (RBBB) or QRS $\geq 120\text{ms}$. 7. Heart Rate: < 50 bpm or > 100 bpm, as determined by vital signs pulse over 30-60 seconds. a) Subjects with a resting heart rate of < 50 bpm will have it repeated once after 5 minutes in the supine position, and if it remains < 50 bpm during the repeat, they will be considered a screen failure. b) Subjects with a rate > 100 bpm should be considered a screen failure. Rescreening may be possible with the approval of the medical monitor, after medical or alternative management of the atrial fibrillation. 8. Kidney Function: Estimated glomerular filtration rate ≤ 44 mL/min/1.73 m² at screening.		

Name of Sponsor/Company: Trevi Therapeutics, Inc.	Study Number: NAL03-202	Protocol Amendment 2
9. Liver Function: Total Bilirubin >3mg/dL [>50umol/L] and Serum Albumin <2.8g/dL at screening. 10. History of major psychiatric disorder, which in the opinion of the Investigator, could interfere with the assessment of anti-cough efficacy and/or safety events during the study or with the ability of the subject to cooperate with study requirements. 11. History of substance abuse, including excessive alcohol consumption, that in the opinion of the investigator, may interfere with the conduct of the study. Alcohol consumption should be limited for the duration of study treatment. 12. Significant medical condition or other factors as assessed by the investigator that may interfere with the subject's ability to successfully complete the study. 13. Pregnant or lactating female subject. Women of childbearing potential (WOCBP) must use an acceptable method of birth control and have a negative pregnancy test at the screening and baseline visits. WOCBP and acceptable methods of birth control are defined in the protocol, <i>Section 8.13 WOCBP Pregnancy test, and contraceptive counselling</i>. 14. Known intolerance (gastrointestinal, central nervous system symptoms), hypersensitivity, drug allergy following the use of an opioid drug. 15. Known hypersensitivity to nalbuphine or to NAL ER excipients. 16. Concurrent or anticipated enrollment in an ongoing interventional clinical trial. Observational or long-term safety follow-up studies (e.g., in a vaccine study) may be allowed upon medical monitor approval.		
<u>Medication-related Exclusions</u> Refer to protocol <i>Section 8.6.1 Prohibited and Restricted Medications, and Washout</i>. 17. Use of opiates is prohibited within 14 days prior to the baseline visit. This includes opiate-containing anti-cough agents, and naltrexone. Subjects are prohibited from using opioids for the duration of the study. 18. Use of benzodiazepines are prohibited within 14 days prior to the baseline visit and for the duration of the study. 19. Monoamine oxidase inhibitors (MAOIs) including methylene blue (methylthioninium chloride) and the antibiotic linezolid are prohibited within 14 days prior to the baseline visit and for the duration of the study. 20. Use of oral corticosteroid prescribed as cough treatment is prohibited within 4 weeks prior to the baseline visit and for the duration of the study. 21. Exposure to any investigational medication, including placebo, is prohibited within 4 weeks prior to the baseline visit and for the duration of the study. 22. Medications prescribed as cough suppressants are prohibited unless on a stable dose 14-days prior to the baseline visit and are expected to remain on that dose for the duration of the study. 23. Use of medications that affect serotonergic neurotransmission and that when used concomitantly with opioids can increase the risk of serotonin syndrome are prohibited unless on a stable dose 14-days prior to the baseline visit and are expected to remain on that dose for the duration of the study. 24. Anti-fibrotic medications are prohibited unless on a stable dose for 8 weeks prior to the baseline visit and are expected to remain on that dose for the duration of the study. 25. Strong inhibitors/inducers of the P450 Isozymes are prohibited unless on a stable dose for 14-days prior to baseline visit and are expected to remain on that dose for the duration of the study.		

Name of Sponsor/Company: Trevi Therapeutics, Inc.	Study Number: NAL03-202	Protocol Amendment 2
26. Use of a medication having a “known risk” of Torsade de Pointes (TdP) categorized as “KR” on the <i>Credible Meds® website</i>, is prohibited within 4 weeks prior to the baseline visit and for the duration of the study. Medications associated with a potential risk of QT prolongation, but not clearly associated with TdP, are permitted at study entry if the following criteria are met: • Subject has been given medication at stable doses for a full 4 weeks prior to baseline. • Medication dose will not be increased after baseline, or during the study, and it is anticipated that the subject will receive the medication for the entirety of the study.		
Statistical Methods: Efficacy The primary efficacy 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. Additional details on the missing data imputation will be provided in the statistical analysis plan (SAP). A hierarchical procedure will be used to control the overall Type I error rate at 0.05 for the primary endpoint and the secondary endpoints across the 3 Nalbuphine dose regimens versus placebo. Each hypothesis will be formally tested only if the preceding hypothesis is significant at the 2-sided 0.05 significance level. The hierarchical testing order will be described in the SAP. Safety The incidence of adverse events will be summarized through the presentation of proportions by Medical Dictionary for Regulatory Activities (MedDRA) body system classification and preferred term. Vital signs, laboratory data, spirometry, physical examinations, and SOWS will be summarized using descriptive statistics. The extent and duration of use of prohibited or restricted medications will be similarly summarized using descriptive statistics. No formal statistical analysis will be performed on safety outcomes; inferences, if any, will be derived through clinical review and interpretation, except where an analysis would be dictated by a secondary endpoint. Additional descriptive narratives will be collected for relevant adverse events to support an eight-factor analysis. ECGs will be reviewed locally for safety. ECGs will be read centrally by specially trained staff and once the database is complete, ECG data (e.g., heart rate, PR, QTcF intervals) will be presented in listings by subject and summarized by collection date and time. A complete ECG assessment will be documented in a separate report from the central ECG specialist vendor. Pharmacokinetics Nalbuphine (parent and/or metabolites) plasma concentration data will be listed by collection time and nalbuphine dose where applicable. Additional pharmacokinetic/pharmacodynamic (PK/PD) analysis may be conducted if data allows and will be presented in an ad-hoc report.		

Name of Sponsor/Company: Trevi Therapeutics, Inc.	Study Number: NAL03-202	Protocol Amendment 2
Sample Size and Power: 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, and are slightly conservative in comparison to a previous study of Nalbuphine ER in 24-hour cough frequency (data on file). A total of approximately 160 subjects will be randomized to account for a potential 30% dropout rate. Efficacy analyses will be based primarily on the mITT population, which consists of all subjects who received at least a dose of study drug. 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; if the SSRE indicates a sample size increase is necessary for the 108mg arm to retain power, all arms (including the 27 mg and 54 mg arms) will be equally increased in order to allow for equal information gathering on all doses. 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).		

1.2 Schedule of Events

Table 1 Schedule of Events

Treatment Day/Week (visit window)	Screening	Baseline	Titration		Fixed Dose Treatment Period		DC ⁸	FU/ EOS ⁹
	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

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 [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.

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).

TABLE OF CONTENTS

CLINICAL TRIAL PROTOCOL: NAL03-202	1
PROTOCOL AMENDMENT SUMMARY OF CHANGES	2
1 PROTOCOL SYNOPSIS	8
1.1 Synopsis	8
1.2 Schedule of Events	16
TABLE OF CONTENTS	19
LIST OF ABBREVIATIONS	23
2 INTRODUCTION.....	26
2.1 Background Information on Idiopathic Pulmonary Fibrosis	26
2.2 Background Information on Nalbuphine.....	26
2.3 Rationale for Investigation of Nalbuphine in Cough Related to Idiopathic Pulmonary Fibrosis and Its Impact on Other Clinical Aspects of IPF	27
2.4 Rationale for Study Design	28
2.5 Risk/Benefit and Ethical Assessment.....	29
3 STUDY OBJECTIVES AND ENDPOINTS	32
3.1 Primary Objective and Endpoint:	32
3.2 Key Secondary Objective and Endpoint:	32
3.3 Secondary Objectives and Endpoints:	32
4 INVESTIGATIONAL PLAN	35
4.1 Study Duration and Dates	35
4.2 Overall Study Design and Plan	35
4.2.1 Study Schematic.....	36
5 STUDY POPULATION SELECTION.....	37
5.1 Study Population and Sites	37
5.2 Inclusion Criteria.....	37
5.3 Exclusion Criteria.....	37
6 STUDY TREATMENT	40
6.1 Description of Treatment(s)	40
6.1.1 Study Drug	40
6.1.2 Placebo	40
6.2 Treatments Administered	40
6.2.1 Dosing Scheme	40
6.3 Dispensing and Intake Instructions	41
6.4 Subject Compliance and Accountability	41
6.5 Multiple Missed Doses.....	41
6.6 Randomization and Blinding.....	42
6.7 Investigational Product Supplies Management	42

6.7.1	Packaging and Labeling	42
6.7.2	IP Storage	42
6.7.3	Accountability	42
7	ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS	43
7.1	Adverse Event Definition.....	43
7.2	Reporting of Adverse Events	43
7.2.1	Events Exempt from Adverse Event Reporting	44
7.2.2	Adverse Events Requiring Additional Narratives	44
7.2.3	Timing	45
7.2.4	Severity Grading	45
7.2.5	Relationship to Study Drug.....	46
7.3	Serious Adverse Events.....	46
7.3.1	Serious Adverse Event Definition.....	46
7.3.2	Reporting Serious Adverse Events to the Sponsor.....	47
7.3.3	Regulatory Aspects of SAE Reporting.....	47
7.4	Pregnancy	48
7.5	Overdose	48
7.6	Independent Data Safety Monitoring Board (DSMB)	49
8	STUDY ACTIVITIES AND PROCEDURES	50
8.1	Informed Consent.....	50
8.2	Demographics, Medical History, IPF History.....	50
8.3	Assess subject eligibility against inclusion/exclusion criteria.....	50
8.4	Subject Medication and Symptom Log.....	51
8.5	Adverse Event Assessments.....	51
8.6	Concomitant Medication and Therapy Assessments	51
8.6.1	Prohibited and Restricted Medications, and Washout	51
8.7	Vital Signs, Pulse Oximetry, Weight, Height and BMI.....	53
8.8	Electrocardiogram (ECG).....	53
8.9	Physical Examination	53
8.10	Swallow Test	53
8.11	Clinical Laboratory Tests.....	54
8.12	Blood Sampling for Pharmacokinetics (PK).....	54
8.13	WOCBP Pregnancy test, and contraceptive counselling.....	55
8.14	Diffusing capacity of the lungs for carbon monoxide (DLCO)	55
8.15	Spirometry – Forced Vital Capacity (FVC)	56
8.16	24-Hour Digital Cough Monitor	56
8.17	Patient Reported Outcome (PRO) Questionnaires	56
8.17.1	SOWS (Subjective Opiate Withdrawal Scale)	57

8.18	Clinical Global Impression of Severity and Change (CGI-S, CGI-C).....	58
8.19	Randomization.....	58
8.20	Telephone Contacts.....	58
8.21	Study Drug Dispensing and Compliance Management	58
8.22	Tolerance and Titration Symptoms Management	58
8.23	Premature Discontinuation / Removal of Subjects from the Trial or Study Drug.....	60
8.24	Appropriateness of Measurements	61
9	PLANNED STATISTICAL METHODS.....	62
9.1	General Considerations	62
9.2	Intercurrent Event Handling.....	62
9.2.1	Primary endpoint and key secondary endpoint	62
9.2.2	Other Endpoints.....	62
9.3	Missing Data	63
9.4	Determination of Sample Size	63
9.5	Analysis Populations	63
9.6	Demographics and Baseline Characteristics	64
9.7	Subject Disposition	64
9.8	Concomitant Medication.....	64
9.8.1	Prohibited and Restricted Medications	64
9.9	Efficacy Analyses.....	64
9.9.1	Primary Efficacy Endpoint.....	64
9.9.2	Secondary Efficacy Endpoints	65
9.10	Safety Analyses.....	66
9.10.1	Adverse Events.....	66
9.10.2	Clinical Laboratory Assessments	66
9.10.3	Vital Signs.....	67
9.10.4	Spirometry	67
9.10.5	Physical Examinations	67
9.10.6	Subjective Opiate Withdrawal Scale (SOWS)	67
9.10.7	Electrocardiograms.....	67
9.11	Pharmacokinetics (PK) and Pharmacodynamics (PD) Analysis	67
9.12	Other Assessment or Analysis	67
9.13	Interim Analysis.....	68
10	ADMINISTRATIVE CONSIDERATIONS	69
10.1	Quality Control and Assurance	69
10.2	Investigators and Study Administrative Structure.....	69
10.3	Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval.....	69

10.4	Ethical Conduct of the Study	70
10.5	Patient Information and Consent.....	70
10.6	Patient Confidentiality and Data Protection.....	70
10.7	Study Monitoring	71
10.8	Case Report Forms and Study Records.....	71
10.9	Protocol Violations/Deviations.....	72
10.10	Access to Source Documentation.....	72
10.11	Data Generation and Analysis.....	72
10.12	Retention of Data	73
10.13	Financial Disclosure.....	73
10.14	Publication and Disclosure Policy	73
11	REFERENCE LIST.....	75
	APPENDICES.....	80

LIST OF IN-TEXT TABLES

Table 1	Schedule of Events	16
Table 2	Schedule of Events (SoE) for PROs.....	18
Table 3	Dosing Scheme.....	40
Table 4	Adverse Events Requiring Additional Narratives	45
Table 5	CTCAE Severity Grading	45
Table 6	Adverse Event Relationship to Study Drug	46
Table 7	Prohibited and Restricted Medications, and Washout Period.....	52
Table 8	List of Laboratory Tests	54
Table 9	Patient Reported Outcome (PRO) Tools.....	57

LIST OF IN-TEXT FIGURES

Figure 1	Study Schematic.....	36
----------	----------------------	----

LIST OF APPENDICES

Appendix 1	Sponsor Signature	81
Appendix 2	Investigator's Signature.....	82
Appendix 3	IPF Diagnosis Guidelines ATS/ERS/JRS/ALAT IPF.....	83

LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical and Therapeutic Class
ATS/ERS/ JRS/ALAT	American Thoracic Society / European Respiratory Society / Japanese Respiratory Society / Asociación Latinoamericana de Tórax
BID	twice daily
BMI	body mass index
bpm	beats per minute
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CS-NRS	Cough Severity Numerical Rating Scale
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CV	coefficient of variation
CYP	Cytochrome (P450 enzymes)
DCF	Data Clarification Form
dl	decilitre
DLCO	Diffusing capacity of the lungs for carbon monoxide
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
EOS	End of Study
EQ-5D-5L™	PRO for Quality of Life (not abbreviated)
E-RS®:IPF	Evaluating Respiratory Symptoms in Idiopathic Pulmonary Fibrosis
ESR	Expedited Safety Report
EU	European Union
EXACT®	EXAcerbation of Chronic pulmonary disease Tool Includes the E-RS:IPF respiratory symptom subscales (IPF-Breathlessness, IPF-Cough, IPF-Sputum, and IPF-Chest Symptoms)
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
FU	Follow-Up
g	gram
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
HCG	human chorionic gonadotropin
HCl	hydrochloride
HDL	high-density lipoprotein
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product (Study Drug)
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology (for IP management)
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
IV	intravenous
LCQ®	Leicester Cough Questionnaire
LDL	Low density lipoprotein
L-IPF®	Living with Pulmonary Fibrosis Questionnaires- Impacts and Symptoms
m ²	square meter
MAOIs	monoamine oxidase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mITT	modified intent-to-treat
mL	millilitre
MMRM	Mixed Model for Repeated Measures
ms	millisecond
NAL ER	Nalbuphine Extended-Release tablets
OTC	over-the-counter
oz	ounce
PBO	placebo
PD	pharmacodynamics
PGI-C	Patient Global Impression of Change
PID	Patient Identification Number
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
PP	Per Protocol
PR	interval that extends from P wave onset until start of QRS complex
PRO	Patient Reported Outcome
QD	once a day
QoL	Quality of Life
QRS	complex representing depolarization of ventricles
QT	interval between the start of the Q wave and the end of the T wave
QTcF	the corrected QT interval by Fridericia
RBBB	Right Bundle Branch Block
RR	Interval between two successive R-waves of the QRS
SAE	serious adverse event
SAP	statistical analysis plan
SNRI	serotonin and norepinephrine inhibitor
SoE	Schedule of Events
SOP	standard operating procedure

SOWS	Subjective Opiate Withdrawal Scale
SpO ₂	saturation of hemoglobin with oxygen
SSRE	sample size re-estimation
SSRI	serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TdP	Torsade de Pointes
TEAE	Treatment Emergent Adverse Event
UIP	usual interstitial pneumonia
UK	United Kingdom
umol/l	micromoles per liter
USUBJID	Unique Subject ID
US	United States
WHO	World Health Organization
WOCBP	women of childbearing potential

2 INTRODUCTION

2.1 Background Information on Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is described in an officially endorsed ATS/ERS/JRS/ALAT Clinical Practice Guideline ([Raghu et al, 2018](#); [updated in Raghu et al 2022](#)) as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and defined by the histopathological and/or radiologic pattern of usual interstitial pneumonia (UIP).

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

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

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

As to the natural history of the disease, while there may be some inter-patient variability in the rate of disease progression ([Raghu et al, 2011](#); [Ley et al 2011](#)), IPF has a poor prognosis with median survival of 3.8 years for adults age 65 ([Lederer and Martinez, 2018](#)).

On physical examination, patients have inspiratory crackles, acrocyanosis, and clubbing. On laboratory workup, most patients have a restrictive pattern on pulmonary function testing, exercise-induced oxygen desaturation, and histopathological and/or radiologic pattern of usual interstitial pneumonia (UIP). The UIP is characterized by chest computed tomography radiologic findings of bilateral reticulation and honeycombing that is predominately peripheral and in the lower lobes and is diagnostic of IPF in the proper clinical setting ([Lederer and Martinez, 2018](#)).

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

2.2 Background Information on Nalbuphine

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

The commercially available approved drug product was first marketed in 1979 in the United States (US) as Nubain[®], on which the presently sold generic injectable formulations are based. Approved indications in the US include the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, as a supplement to balanced anesthesia, pre-operative and post-operative analgesia, and obstetrical analgesia during labor and delivery (*Nubain US Prescribing Information, 2023*). Nalbuphine remains an unscheduled drug in the US (*US Drug Enforcement Agency, Jan 2023; US Dept of Justice List of Scheduling for Controlled Substances, 2023*).

Commercial availability in the European Union (EU) of the parenteral formulation of nalbuphine dates to 1986 (*Medicines Evaluation Board in the Netherlands, 2010*) when the originator product, Nubain 10 mg/ml solution for injection, was registered in the Netherlands by Bristol-Myers Squibb. In 2020, an application from Altamedics GmbH for Nubain 10 mg/ml Injektionslösung was approved in Germany, Austria, and the Netherlands for the short-term relief of moderate to severe pain and for pre- and post-operative analgesia (*Nubain Public Assessment Report, 2020*). Nalbuphine is not listed in the List of Narcotic Drugs Under International Control in accordance with the United Nations Single Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol (*List of Psychotropic Substances Under International Control, 2022*).

Nalbuphine is a member of the opioid agonist-antagonist class of drugs with agonistic action at kappa opioid receptors and antagonistic activity at mu opioid receptors (*Yaksh and Wallace 2011*). In addition to a prior phase 2 study in IPF related cough (Clinical Study TR12), the clinical development program of NAL ER tablets has included prior investigational studies for the treatment of prurigo nodularis related pruritus, uremic pruritus in hemodialysis patients as well as safety and efficacy analgesic studies. Additional information can be found in the Investigator's Brochure (IB).

2.3 Rationale for Investigation of Nalbuphine in Cough Related to Idiopathic Pulmonary Fibrosis and Its Impact on Other Clinical Aspects of IPF

A summary of the rationale for investigating the use of nalbuphine in cough related to IPF is provided below. Additional information is available in the IB.

There is medical literature reporting that the opioid drug class may be effective antitussives. Morice et al. state that in chronic cough subjects, morphine may be effective treatment (*Morice et al, 2007; Morice et al, 2020*). Nalbuphine has been shown in human studies to have preventative antitussive effect on acute cough during anesthesia induction (*Wang et al, 2020*). Other mixed agonist-antagonist pharmacologic class of drugs have also been shown to be effective in managing the adverse effect of acute cough during anesthesia induction (*Ai et al, 2010; Cheng et al, 2016*). The mixed agonist-antagonist butorphanol has been approved as an animal anti-tussive (*Torbutrol[®] US Package Insert, 2013*).

The physiological phenomena of central sensitization of cough may be occurring in IPF as an explanation of the chronic nature of the cough (*Hope-Gill et al, 2003*). Integration of cough reflex behavior that occurs at brainstem level (*Canning et al, 2014*) may be modulated by nalbuphine pharmacologic action given the high density of opiate receptors (*Volkow and McLellan, 2016*) Opiate receptors in the cerebrum may also potentially be

modulated by nalbuphine pharmacologic action where cortical mediated control of cough is an important regulator of the cough reflex set point ([Mazzone et al, 2009](#))

Mahler and O'Donnell discuss the role of cortical activity in the sensation of dyspnea ([Mahler and O'Donnell, 2015](#)), and Jennings et al and Mahler discuss the use of opioids in the treatment of dyspnea ([Jennings et al, 2002](#); [Mahler, 2013](#)). Thus, the pharmacologic action of nalbuphine may be helpful in modifying the dyspnea related perception of air hunger ([Parshall et al, 2012](#)). In addition, improvement in breathlessness may be achieved by lessening the biomechanical work done by thoracic musculature as a result of reducing the frequency of coughing.

A further potential site of pharmacologic action of nalbuphine may be at the peripheral nerve level ([Volkow and McLellan, 2016](#)) innervating pulmonary structures or the intrinsic opiate receptors located in lung tissue ([Zebraski et al, 2000](#); [Krajnik et al, 2014](#)).

2.4 Rationale for Study Design

The primary study endpoint, change in 24-hour cough frequency (coughs per hour), will be analyzed by use of an objective digital recording device, consistent with the recommendations of Boulet et al who summarized the CHEST Expert Panel recommendations regarding tools to be used in clinical trials assessing cough ([Boulet et al, 2015](#)). The Panel recommended that acoustic cough counting to assess cough frequency should be done through objective means. Secondly, as supported by the development work of Bacci et al, the E-RS:IPF scoring of the EXACT daily diary tool will be used as a patient-reported outcomes (PRO) instrument in assessing NAL ER tablets efficacy in reducing IPF-related cough ([Bacci et al, 2018a; 2018b](#)).

The patients participating in the FDA's "The Voice of the Patient" reported that in addition to cough, the symptoms of shortness of breath and fatigue had the greatest impact on their daily life (["The Voice of the Patient" series report on Idiopathic Pulmonary Fibrosis; page 5-7; March 2015](#)). Based on this information, and the mechanism of action of NAL ER tablets, these additional symptoms may be amenable to treatment and will be investigated with secondary endpoint metrics.

The FDA's "The Voice of the Patient" mentions that dyspnea is an interchangeable clinical term with breathlessness and describes patients' experience of breathlessness as a symptom, with no distinction in the descriptions being made as to the occurrence of breathlessness with physical activity or breathlessness occurring at rest (["The Voice of the Patient" series report on Idiopathic Pulmonary Fibrosis; page 5-7; March 2015](#)). Bacci et al distinguishes between breathlessness and dyspnea within a breathing status E-RS subscale ([Bacci et al 2018b](#)). Dyspnea is defined in terms of severity of breathlessness with activity. This breathing related subscale will be used to analyze whether the concepts of breathlessness associated with or without physical activity can be both or separately affected by NAL ER treatment. The EQ-5D-5L™ Quality of Life PRO will be used as an additional metric in assessing investigational product efficacy in reducing this burdensome symptom of IPF.

The TR12 study was a randomized, double-blind, placebo (PBO)-controlled, crossover trial with two 22-day treatment periods (1: NAL ER-PBO; 2: PBO-NAL ER) separated by a 2-week washout using an objective digital monitor (VitaloJAK). Subjects treated with doses escalating to 162 mg BID of NAL ER showed a 76.1% improvement (95% CI, -83.1 to -69.1) in the geometric mean percent change in objective cough frequency compared with 25.3%

(95% CI, -43.9 to -6.7) in placebo-treated subjects, with a 50.8% placebo-adjusted change ($P < 0.0001$).

The purpose of this present study is to evaluate the dose response relationship between 3 doses of NAL ER (27, 54, 108 mg BID) and placebo.

Centrally active drugs are typically titrated in order to minimize the incidence and severity of AEs that can occur with drug initiation; thus, NAL ER is titrated to the target dose of the respective randomized study arm (see [Table 3 Dosing Scheme](#)). The AEs most commonly associated with titration involve the central nervous system (CNS) (nausea, headache and dizziness) and gastrointestinal (nausea and vomiting) organ systems (see [Section 8.22 Tolerance and Titration Symptoms Management](#)). A similar titration rate of NAL ER has been safely used in the previous IPF phase 2 TR12 study and in other study populations (see IB for details). In addition, the titration rate is consistent with opioid class guidelines such as the “three-day tolerance check” ([National Opioid Use Guideline Group Canada, 2010](#)) and “five ½ life” rule ([CDC Guideline for Prescribing Opioids for Chronic Pain, 2016](#)). In the TR12 trial subjects were escalated from 27 mg to 54 mg, to 108 mg and then 162 mg dose levels on Days 5, 9 and 16. In the present study, subjects will be escalated from 27 mg to 54 mg and then to 108 mg on Days 7 and 14 in the high dose group.

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

As there are currently no approved pharmacological therapies for the treatment of cough related to IPF, the use of placebo is acceptable in the current design, in accordance with the Declaration of Helsinki ethical principles for medical research.

2.5 Risk/Benefit and Ethical Assessment

Nalbuphine is currently in medical use as a parenteral formulation ([Nalpain UK package insert, 2011](#); [Nubain US Prescribing Information, 2019](#)) indicated for analgesia management as well as in the US as a supplement to anesthesia. The highest dose proposed in the current clinical study is 108 mg BID (216 mg daily dose), well below the highest recommended daily treatment of 144 mg IV dose (equivalent to 864 mg oral dose) for the currently available parenteral administered product. The high peak plasma concentrations that occur in the setting of parenteral use significantly exceed the peak levels observed with NAL ER oral dosing, an observation that is reassuring with respect to the potential for severe, acute toxicity.

Opiate drug class-related concerns such as the potential for physical dependence, linked to long-term use of opiates, is acknowledged. A requirement for completion of a 2-week safety observation period with daily Subjective Opiate Withdrawal Scale (SOWS) reporting has been incorporated into the study.

The TR12 study in patients with IPF-associated chronic cough demonstrated that subjects treated with doses escalating to 162 mg BID of NAL ER showed a 76.1% improvement (95% CI, -83.1 to -69.1) in the geometric mean percent change in objective cough frequency compared with 25.3% (95% CI, -43.9 to -6.7) in placebo-treated subjects, with a 50.8% placebo-adjusted change ($P < 0.0001$). In TR12, cough PRO measurements, including daily

EXACT2 Cough Frequency Scores and the CS-NRS measure of cough severity, revealed large cough effect size reductions early in the dose titration design, with near maximal effects on cough PROs seen when subjects were taking the 54 mg BID dose of NAL ER. The 108 mg BID dose of NAL ER in TR12 produced similar effects to those of the 162 mg BID dose level, so dosing in the CORAL study was capped at the 108 mg BID level.

The potential for NAL ER to cause respiratory depression and the increased risk this may pose in an IPF population is an important consideration. Opioids are known to induce respiratory depression *via* activation of μ -opioid receptors in the CNS ([Ramirez 2021](#)). Whereas full μ -opioid agonists like morphine and fentanyl affect breathing in a dose-dependent manner leading to severe hypoxia and fatal respiratory depression, the respiratory depression effect for partial opioid agonists such as nalbuphine is dose-limited. The prescribing information for parenterally administered nalbuphine states that the drug may produce the same degree of respiratory depression as an equianalgesic dose of morphine; it also states that the drug exhibits a ceiling effect such that increases in dose greater than 30 mg nalbuphine HCl salt (27 mg free base) do not produce further respiratory depression in the absence of other CNS active medications affecting respiration. ([Nubain US Prescribing Information, 2019](#)). Investigations reported a ceiling effect for respiratory depression following IV administration at doses in excess of 30 mg/70 kg ([Romagnoli 1978](#); [Gal 1982](#); [Romagnoli 1980](#); [Pugh 1989](#)). The distinction between morphine and nalbuphine pharmacology was noted in anesthetized patients who are known to have an increased sensitivity to respiratory depression effects. An elective surgery subject population ([Klepper 1986](#)) demonstrated that nalbuphine HCl in doses of 4.5 to 50 mg/70 kg IV (equivalent to 4-45 mg/70 kg free base) co-administered with a premedication of either diazepam 0.16/kg or lorazepam 0.06/kg followed by thiopentone, 66% nitrous oxide and 1% halothane had a dose limiting effect on minute ventilation and end-tidal CO₂ concentration endpoints, with no evidence of apnea at any dose studied. In this study morphine administered in the range 3 to 17.5 mg/70 kg IV, demonstrated no dose-limiting effects on minute ventilation and end-tidal CO₂, and the highest dose of the drug led to respiratory impairment that progressed to apnea in two subjects. Thus, the ceiling effect for respiratory depression by intravenous nalbuphine provides a significant pharmacological differentiation compared to other opioids.

Regarding orally dosed NAL ER, route of administration is also likely to affect the risk for respiratory depression, as peak plasma concentrations that occur in the setting of parenteral use significantly exceed the peak levels observed with NAL ER oral dosing, and additionally, oral bioavailability of NAL ER is approximately 16%. Based on the safety data obtained to date in the study populations investigated with oral NAL ER, no safety signals related to respiratory function impairment have been identified. These safety datasets include the TR12 study in IPF patients studied with doses of up to 162 mg of NAL ER, compared to the maximal dose of 108 mg NAL ER planned for this study.

Of note, is the safety data obtained with NAL ER Phase 1 studies, including investigations conducted in study populations with marked renal and hepatic conditions. Review of five clinical studies (NAL02, NAL06, TR01, TR08 and TR10) conducted by the Sponsor in which individual subject respiratory parameters were closely monitored (i.e., with serial respiratory values as a function of time) indicated that the SpO₂ and RR parameters did not demonstrate a pattern of respiratory function effects even when NAL ER was administered at supratherapeutic doses. TR08 was a double-blind, placebo-controlled study meant to evaluate

the human abuse potential of nalbuphine in recreational drug users. TR08 provided a good opportunity to evaluate dose-response for vital sign parameters over seven doses ranging between 81 mg and 486 mg, the widest range of doses evaluated in clinical studies. In the TR08 study nalbuphine was administered as a solution in order to emphasize the C_{max} effect as compared to NAL ER, and so the early exposure profile was closer to that seen with parenteral nalbuphine. The 486 mg supratherapeutic dose was 4.5-fold higher than the planned 108 mg high dose in the CORAL study and is equivalent to ~ 70 mg IV dose when adjusted for a 16% bioavailability. Analysis confirmed the lack of effect of nalbuphine on change from pre-dose in vital parameters, including respiratory parameters SpO2 and RR, and that increasing the dose from 81 mg to 486 mg did not show a dose response in the degree of change.

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

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

In summary, the risk for subjects participating in this study is judged to be low based on previous experience with oral administration of NAL ER, including the TR12 study in IPF patients studied with doses of up to 162 mg BID of NAL ER. The current study will utilize a low initiation dose of 27 mg QD, and a gradual dose titration up to a maximal dose of 108 mg BID in the high dose group. Careful safety monitoring of subjects will be performed during the clinical study. Investigators will be educated regarding the symptoms of rare but significant Aes that are linked to the opiate class.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective and Endpoint:

Objective	Endpoint
Effect of NAL ER on 24-hour cough frequency (coughs per hour) at Week 6 using objective digital cough monitoring.	Relative change from Baseline in 24-hour cough frequency (coughs per hour) at Week 6 for NAL ER compared with placebo.

3.2 Key Secondary Objective and Endpoint:

Objective	Endpoint
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 .	Relative change from Baseline in the E-RS:IPF Cough subscale at Week 6 for NAL ER compared with placebo.

3.3 Secondary Objectives and Endpoints:

Objective	Endpoint
Safety and tolerability of NAL ER in the study population	- Adverse events, clinical laboratory assessments, vital signs, spirometry and physical examination summaries. - ECG summaries [ECGs will be analyzed in a separate report]. - Subjective Opiate Withdrawal Scale (SOWS) daily summaries for the 14 days following the last dose of investigational product.
24-hour cough frequency (Coughs per hour).	- Relative change from Baseline in 24-hour cough frequency (coughs per hour) at Week 2, 4, and 6, for NAL ER compared with placebo. - Proportion of responders with $\geq 30\%$, $\geq 50\%$ and $\geq 75\%$ 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.

Objective	Endpoint
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 (Evaluating Respiratory Symptoms in Idiopathic Pulmonary Fibrosis) and subscales as collected in the EXACT® (EXAcerbation of Chronic pulmonary disease Tool)	- Change from Baseline in the E-RS: IPF Cough subscale at Week 1, 2, 3, 4, 5, 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. - 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)	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 and domain scores (physical, psychological, and social domains)	- 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® (Living with Pulmonary Fibrosis Impacts Questionnaire)	Change from Baseline in the L-IPF at Week 6, for NAL ER compared with placebo.
L-IPF® (Living with Pulmonary Fibrosis Symptoms Questionnaire)	Change from Baseline in the L-IPF and its domains at Week 6, for NAL ER compared with placebo.
EQ-5D-5L™	Change from Baseline in the EQ-5D-5L™ at Week 6, for NAL ER compared with placebo.

Objective	Endpoint
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 post-baseline 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 post-baseline timepoint for NAL ER compared with placebo.
CGI-S, CGI-C (Clinical Global Impression of Severity and 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.

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

4 INVESTIGATIONAL PLAN

4.1 Study Duration and Dates

The planned study period is from

- Estimated **first subject randomized in Oct 2023**, until
- Estimated **last subject completed in Dec 2024**,

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

The duration of participation for each subject will be up to 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 / EOS:** 14 (+3) days after the last study treatment administration.

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

4.2 Overall Study Design and Plan

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

After meeting eligibility during the Screening Period, subjects will be randomized (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 [Table 3 Dosing Scheme](#), 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 Study Schematic](#), and [Section 1.2 Schedule of Events](#), [Table 1](#) and [Table 2](#).

If permanent discontinuation of investigational product occurs the discontinuation and safety follow-up/EOS visits should be performed. The subject will then be contacted at the calculated timepoint of Week 6 (42 days post baseline) by phone to collect information on serious adverse events (SAEs) and vital status.

4.2.1 Study Schematic

Figure 1 Study Schematic

Screening Period	Titration Period		Fixed dose period				Washout Period
			NAL ER 108 mg Tablets BID				
			NAL ER 54 mg Tablets BID				
			NAL ER 27 mg Tablets BID				
			Placebo Tablets BID				
Day -1 1:1:1:1 Randomization or Screen Failure						Week 6 Primary End Point	
Week -4 Day -1	Week 1 Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	

5 STUDY POPULATION SELECTION

5.1 Study Population and Sites

Approximately 160 subjects with diagnosed IPF will be randomized, across approximately 75 centers globally.

The number of subjects may be adjusted based on a Sample Size Re-Estimation (SSRE).

5.2 Inclusion Criteria

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

1. **Diagnosis of IPF** as determined by the Investigator based on ATS/ERS/JRS/ALAT guidelines (*Raghu et al, 2018; updated in Raghu et al 2022*).
2. **Cough Severity Score ≥ 4** on CS-NRS (Cough Severity Numerical Rating Scale) during the Screening period and Baseline.
3. History of **chronic cough** for at least 8 weeks before screening.
4. **SpO₂ $\geq 92\%$** , taken after at least 5 minutes in a sitting position, undisturbed and non-stimulated (Saturation of Hemoglobin with Oxygen as Measured by Pulse Oximetry).
5. **FVC $\geq 40\%$** predicted of normal – Force Vital Capacity, as determined by spirometry adhering to ATS/ERS guidelines (*Graham et al, 2019*).
6. **DLCO $\geq 25\%$** predicted of normal – Diffusing capacity of the lungs for carbon monoxide corrected for hemoglobin, assessed within the last 12 weeks, or at the time of screening.
7. Males or females ages 18 years and older at the time of consent.
8. Willing and able to provide written informed consent, comply with study requirements and restrictions, and agree to the confidential use and storage of all data and use of all anonymized data for publication including scientific publication.

5.3 Exclusion Criteria

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

1. Currently on **continuous oxygen therapy for longer than 16 hours** at any level or delivered by any modality. Intermittent oxygen use of any duration over any given 24-hour period is allowed.
2. Inadequate **swallow reflex** as assessed by the ability to sip 3 fluid oz (or 90 mL) of water without coughing or choking.
3. Upper or lower **respiratory tract infection** in the last 8 weeks prior to the baseline visit.
4. Clinical history of **aspiration pneumonitis**.
5. Diagnosis of **sleep apnea**.

6. **Cardiac Safety:** Mean QTcF value of 3 centrally read screening electrocardiograms (ECGs) calculated as
 - a) $\geq 470\text{ms}$ if QRS $< 120\text{ms}$ or
 - b) $\geq 500\text{ms}$ in the presence of either a Right Bundle Branch Block (RBBB) or QRS $\geq 120\text{ms}$.
7. **Heart Rate:** $< 50\text{ bpm}$ or $> 100\text{ bpm}$, as determined by vital signs pulse over 30-60 seconds
 - a) Subjects with a resting heart rate of $< 50\text{ bpm}$ will have it repeated once after 5 minutes in the supine position, and if it remains $< 50\text{ bpm}$ during the repeat, they will be considered a screen failure.
 - b) Subjects with a rate $> 100\text{ bpm}$ should be considered a screen failure. Rescreening may be possible with the approval of the medical monitor, after medical or alternative management of the atrial fibrillation.
8. **Kidney Function:** Estimated glomerular filtration rate $\leq 44\text{ mL/min/1.73 m}^2$ at screening.
9. **Liver Function:** Total Bilirubin $> 3\text{mg/dL}$ [$> 50\text{umol/L}$] and Serum Albumin $< 2.8\text{g/dL}$ at screening.
10. History of major **psychiatric disorder**, which in the opinion of the Investigator, could interfere with the assessment of anti-cough efficacy and/or safety events during the study or with the ability of the subject to cooperate with study requirements.
11. History of **substance abuse**, including excessive alcohol consumption, that in the opinion of the investigator, may interfere with the conduct of the study.
Alcohol consumption should be limited for the duration of study treatment.
12. **Significant medical condition** or other factors as assessed by the investigator that may interfere with the subject's ability to successfully complete the study.
13. **Pregnant or lactating** female subject. Women of childbearing potential (WOCBP) must use an acceptable method of birth control and have a negative pregnancy test at the screening and baseline visits. WOCBP and acceptable methods of birth control are defined in the protocol,
Section 8.13 WOCBP Pregnancy test, and contraceptive counselling.
14. Known **intolerance** (gastrointestinal, central nervous system symptoms), hypersensitivity, drug allergy following the use of an opioid drug.
15. Known hypersensitivity to nalbuphine or to NAL ER excipients.
16. Concurrent or anticipated enrollment in an **ongoing interventional clinical trial**. Observational or long-term safety follow-up studies (e.g., in a vaccine study) may be allowed upon medical monitor approval.

Medication-related Exclusions

Refer to protocol [Table 7 Prohibited and Restricted Medications, and Washout Period](#).

17. Use of **opiates** is prohibited within 14 days prior to the baseline visit. Includes opiate-containing anti-cough agents, and naltrexone. Subjects are prohibited from using opioids for the duration of the study.
18. Use of **benzodiazepines** are prohibited within 14 days prior to the baseline visit and for the duration of the study.
19. **Monoamine oxidase inhibitors** (MAOIs) including methylene blue (methylthioninium chloride) and the antibiotic linezolid are prohibited within 14 days prior to the baseline visit and for the duration of the study.
20. Use of **oral corticosteroid prescribed as cough treatment** is prohibited within 4 weeks prior to the baseline visit and for the duration of the study.
21. Exposure to any **investigational medication**, including placebo, is prohibited within 4 weeks prior to the baseline visit and for the duration of the study.
22. Medications prescribed as **cough suppressants** are prohibited unless on a stable dose 14-days prior to the baseline visit and are expected to remain on that dose for the duration of the study.
23. Use of **medications that affect serotonergic neurotransmission** and that when used concomitantly with opioids can increase the risk of serotonin syndrome are prohibited unless on a stable dose 14-days prior to the baseline visit and are expected to remain on that dose for the duration of the study.
24. **Anti-fibrotic medications** are prohibited unless on a stable dose for 8 weeks prior to the baseline visit and are expected to remain on that dose for the duration of the study.
25. **Strong inhibitors/inducers of the P450 Isozymes** are prohibited unless on a stable dose for 14-days prior to baseline visit and are expected to remain on that dose for the duration of the study.
26. Use of a medication having a “known risk” of Torsade de Pointes (TdP) categorized as “KR” on the [Credible Meds® website](#), is prohibited within 4 weeks prior to the baseline visit and for the duration of the study.

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

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

6 STUDY TREATMENT

6.1 Description of Treatment(s)

6.1.1 Study Drug

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

6.1.2 Placebo

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

6.2 Treatments Administered

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

For subjects assigned to one of the NAL ER arms, the dose will be titrated from a starting dose of 27 mg QD to the target dose of 27 mg or 54 mg or 108 mg BID over the first 2 weeks of the treatment period. Then the subject will receive the fixed dose until the end of the study dosing period at Week 6.

6.2.1 Dosing Scheme

Table 3 Dosing Scheme

Study Day / Week	NAL ER 27 mg BID		NAL ER 54 mg BID		NAL ER 108 mg BID		Placebo Arm	
	AM	PM	AM	PM	AM	PM	AM	PM
1	-	27	-	27	-	27	-	Placebo
2	-	27	-	27	-	27	-	Placebo
3	27	27	27	27	27	27	Placebo	Placebo
4	27	27	27	27	27	27	Placebo	Placebo
5	27	27	27	27	27	27	Placebo	Placebo
6	27	27	27	27	27	27	Placebo	Placebo
7	27	27	27	54	27	54	Placebo	Placebo
8	27	27	54	54	54	54	Placebo	Placebo
9	27	27	54	54	54	54	Placebo	Placebo
10	27	27	54	54	54	54	Placebo	Placebo
11	27	27	54	54	54	54	Placebo	Placebo
12	27	27	54	54	54	54	Placebo	Placebo
13	27	27	54	54	54	54	Placebo	Placebo
14	27	27	54	54	54	108	Placebo	Placebo
Week 3- Week 6	27	27	54	54	108	108	Placebo	Placebo

6.3 Dispensing and Intake Instructions

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

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

If less than 8 hours until the next planned dose, the subject should skip the dose.

Subjects will be informed that the investigational product may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the titration period and in combination with alcohol or tranquilizers or other pharmacologic CNS depressants. Subjects will be instructed not to drive or operate machinery unless they are tolerant to the drug and know how they will react to the medication, and to limit alcohol consumption for the duration of study treatment.

6.4 Subject Compliance and Accountability

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

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

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

Compliance will be monitored:

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

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

For compliance over 100% and the definition of overdose, refer to [Section 7.5 Overdose](#).

6.5 Multiple Missed Doses

If the subject misses 3 or more consecutive doses (equivalent to approximately 1.5 days), contact the study Medical Monitor to discuss the situation and, if needed, dosing instructions

(See also *Section 8.22 Tolerance and Titration Symptoms Management* and *8.23 Premature Discontinuation / Removal of Subjects from the Trial or Study Drug*). Subjects should never take additional doses of investigational product to make up for missed doses. If investigational product is being restarted after missed doses, the subject should be instructed not to remove the tablets from the days and/or time points on which investigational product was missed; these tablets are to remain in the blister card.

6.6 Randomization and Blinding

Randomization will be performed, and blinding maintained, via IRT. Upon confirmation of eligibility by the study site and completion of all scheduled procedures at the Baseline (Day - 1) visit, subjects will be randomized in a 1:1:1:1 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.

A DSMB will be provided unblinded data for safety review. Unblinded data will be restricted to DSMB members and the designated unblinded team.

6.7 Investigational Product Supplies Management

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

6.7.1 Packaging and Labeling

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

6.7.2 IP Storage

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

The Investigator must ensure that all investigational product supplies are kept in a secure locked area, under controlled temperature, with access limited to those authorized by the Investigator.

6.7.3 Accountability

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

7 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Subjects will be closely monitored for safety throughout the study. In addition to adverse events, vital signs including pulse oximetry, ECGs reviewed by investigator, physical examinations, spirometry, and clinical laboratory testing will be conducted to monitor subject safety. To monitor for possible withdrawal symptoms, subjects will complete the SOWS daily for 14 days following the last dose of investigational product. Details of assessments are provided in [Section 8 Study Activities and Procedures](#).

7.1 Adverse Event Definition

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation subject reported on or after the first screening date. A Treatment Emergent Adverse Event (TEAE) is any untoward medical occurrence in a clinical investigation subject or subject administered a pharmaceutical product on or after the initial administration of investigational product and which does not necessarily have a causal relationship with treatment. The Investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

The AE may be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom whether or not related to the medicinal (investigational) product, or disease temporally associated with the use of a medicinal (investigational) product
- A new illness
- Worsening of a pre-existing condition
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the investigational product, including comparator
- A combination of two or more of these factors

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

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

7.2 Reporting of Adverse Events

All AEs occurring during the study will be collected on the AE eCRF. Non-serious adverse events related to ECG, laboratory, or physical examination findings during Screening (i.e., after the signing of the informed consent form and prior to the first dose of IP) are to be recorded on the Medical History eCRF unless considered to be caused by a study procedure in which case they are to be recorded on the Adverse Event eCRF.

All serious adverse events and non-serious adverse events other than those described above with an onset during Screening should be recorded on the Adverse Event eCRF. All Adverse

Events with onset after exposure to any amount of study drug are to be recorded on the Adverse Event eCRF.

Starting from the point when the subject signs the Informed Consent Form (ICF), and continuing for the duration of the study, subjects must be instructed to record any new Aes on the study specific symptom log. Subjects should bring the log to every clinic visit, where it will be retrieved for review by study staff prior to re-dispensing it (or issuing a new log) to the subject.

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

Aes that have not been directly reported to the Investigator will be promptly conveyed to the Investigator by the study staff. Investigators will additionally review any AE source documents and the subject's medical records, on a regular basis during the study.

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

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

Clinically significant worsening in procedures such as physical examination, vital sign, and ECG following the start of investigational product treatment will be recorded as adverse events.

7.2.1 Events Exempt from Adverse Event Reporting

As cough is an endpoint in this study, it will NOT be reported as an adverse event. Refer to [Section 8.16 24-Hour Digital Cough Monitor](#) and [Section 8.17 Patient Reported Outcome \(PRO\) Questionnaires](#) for additional details regarding data collection for cough.

7.2.2 Adverse Events Requiring Additional Narratives

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

Table 4 Adverse Events Requiring Additional Narratives

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

7.2.3 Timing

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

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

Any (S)AE still unresolved at the safety follow-up/EOS or premature discontinuation visit will be followed by the Investigator for at least 30 days from the last dose of investigational product.

All unresolved Aes that were reported by the Investigator to be probably drug related should be followed until the events are resolved/stabilized, the subject is lost to follow-up, or the AE is deemed irreversible.

7.2.4 Severity Grading

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

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

Table 5 CTCAE Severity Grading

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

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

7.2.5 Relationship to Study Drug

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

Table 6 Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Definitely related	- Follows a reasonable temporal sequence from administration of the study intervention - Follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping. - Reappearance of the event on repeated exposure that could not be reasonably explained by the known characteristics of the subject’s clinical state
Probably related	- Follows a reasonable temporal sequence from investigational product administration - Abates upon discontinuation of the investigational product - Cannot be reasonably explained by the known characteristics of the subject’s clinical state
Possibly related	- Follows a reasonable temporal sequence from investigational product administration - could have been produced by the subject’s clinical state or by other modes of therapy administered to the subject
Unlikely related	- Does not follow a reasonable temporal sequence from investigational product administration - Is readily explained by the subject’s clinical state or by other modes of therapy administered to the subject
Not related	- Clearly not related to the investigational product and another cause of the event is most plausible - A clinically plausible temporal sequence is inconsistent with the onset of the event

7.3 Serious Adverse Events

7.3.1 Serious Adverse Event Definition

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

- death,
- life-threatening AE,
- hospitalization or prolongation of existing hospitalization,

- a persistent or significant disability/incapacity,
- a congenital anomaly/birth defect.

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

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

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

7.3.2 Reporting Serious Adverse Events to the Sponsor

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

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

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

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

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



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

7.3.3 Regulatory Aspects of SAE Reporting

The Investigator will promptly report all SAEs to the Sponsor or their designee within the timeframe specified in [Section 7.3.2 Reporting Serious Adverse Events to the Sponsor](#). Prompt notification of SAEs by the Investigator is essential so that the Sponsor can meet legal

obligations and fulfill ethical responsibilities towards the safety of all subjects participating in their sponsored investigational trials.

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

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

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

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

7.4 Pregnancy

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

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

7.5 Overdose

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

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

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

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

7.6 Independent Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will periodically review safety data. The DSMB will periodically review unblinded study information (on a treatment group level) during the conduct of the study.

8 STUDY ACTIVITIES AND PROCEDURES

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

8.1 Informed Consent

Potential subjects must provide written consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

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

The ICF will be given to the subject to read, and the study will be explained by a qualified member of the study staff. After reading the ICF, the potential subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

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

8.2 Demographics, Medical History, IPF History

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

Clinically significant abnormal findings identified during the screening period for the first time but indicative of an existing condition (e.g., laboratory, physical exam) will be documented in the medical history (See [Section 7.2 Reporting of Adverse Events](#)).

IPF history will include history of smoking, supplemental oxygen usage, and previous IPF and cough treatments.

8.3 Assess subject eligibility against inclusion/exclusion criteria

The Investigator will assess the eligibility of the subject during the screening period and will confirm their eligibility prior to randomizing. At the point that the subject is found not eligible, further screening procedures are not required, and can be documented as not done.

For unique circumstances that may justify rescreening, Investigators may contact the Medical Monitor to discuss and obtain approval for rescreening.

8.4 Subject Medication and Symptom Log

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

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

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

8.5 Adverse Event Assessments

Refer to [Section 7 Adverse Events and Serious Adverse Events](#) for full details on safety management and recording of adverse events.

8.6 Concomitant Medication and Therapy Assessments

Subjects may receive all clinically indicated medications and therapies during the study with the exceptions noted in [Table 7 Prohibited and Restricted Medications, and Washout Period](#).

Any medication or therapy including oxygen therapy, over-the-counter (OTC) medications, herbal medications, vitamins, and nutritional supplements taken and their reason for use will be collected, and recorded in the Concomitant Medication eCRF from **14 days prior to the first day of the screening** until the last safety follow-up/EOS. Anti-fibrotic medications will be documented from 8-weeks prior to baseline.

Each subject will be instructed to report the use of all new or changed medications, including oxygen therapy, over-the-counter (OTC) medications, herbal medications, vitamins, and nutritional supplements on the study specific medication log, and to bring the log to each study visit for review (See [Section 8.4 Subject Medication and Symptom Log](#)). Subjects will also be instructed about the importance of not taking any new medications during the study (including OTC medications) without consulting the Investigator.

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

8.6.1 Prohibited and Restricted Medications, and Washout

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

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

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

Table 7 Prohibited and Restricted Medications, and Washout Period

Medication	Restriction	Washout Period
Opioid Medications, including opiate containing cough suppressants	Prohibited throughout the study	14 days prior to the baseline visit
Opioid antagonists (e.g., naloxone, naltrexone)	Prohibited 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 corticosteroids 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 4 weeks 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
Serotonergic drugs - serotonin reuptake inhibitors (SSRIs), - serotonin and norepinephrine reuptake inhibitors (SNRIs), - tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, - tetracyclic antidepressants, 5-HT2 antagonists	Stable Dose throughout the study, where possible Subjects will be informed of the risk of serotonin syndrome and the potential side effects they should be alert for, in the ICF	Stable dose from 14 days prior to the baseline visit
Strong inhibitors/inducers of the P450 Isozymes as per the current FDA Drug Interactions list*	Stable Dose throughout the study, where possible	Stable dose from 14 days prior to the baseline visit
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-interactions-table-substrates-inhibitors-and-inducers

8.7 Vital Signs, Pulse Oximetry, Weight, Height and BMI

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

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

- Blood pressure: measured with a standard mercury sphygmomanometer, or an automated oscillometric blood pressure monitor.
- Pulse oximetry: Pulse Oximetry will be recorded with finger pulse oximeter device. If the subject has regular oxygen therapy as allowed per the exclusion criteria, they may continue their typical use concurrently to assessment of SpO₂.
- Heart rate
- Respiratory rate
- Body temperature
- Weight
- Height: recorded at screening only, to allow the calculation of BMI.

8.8 Electrocardiogram (ECG)

ECGs are to be performed in triplicate after the subject has been in the supine position for at least 5 minutes with all 3 tracings obtained within a period of 3-10 minutes. Whenever possible, ECG testing should be performed directly prior to the collection blood samples (clinical laboratory and PK samples).

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

ECG intervals (PR, RR, QRS, QT, and QTcF using nomogram table), rate, rhythm, and other clinically significant abnormalities (e.g., left ventricular hypertrophy, pathological Q-waves) will be assessed by the ECG specialist vendor, and a report sent to site within 72 hours of successful transmission.

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

8.9 Physical Examination

This evaluation will be performed by the investigator and include examination of the following body systems: general appearance, eyes, ears, nose, throat, head and neck, chest, and lungs, cardiovascular, abdomen, musculoskeletal, lymphatic, dermatological, neurological, and extremities.

8.10 Swallow Test

Subjects will be asked to drink 3 fluid oz / 90 mL of water uninterrupted and will be evaluated by clinical staff for their ability to swallow during and up to one minute after the completion of the test. This test will be used as a screening assessment to verify adequate swallow reflex and may be repeated, if necessary.

8.11 Clinical Laboratory Tests

Clinical laboratory tests will be performed by a qualified central laboratory. Whenever possible, blood samples are to be obtained after the collection of vital signs and ECG recordings at designated visits. Fasting is not required for routine lab testing. If medically indicated for follow-up of a certain condition or event, fasting labs can be performed.

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

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

Table 8 List of Laboratory Tests

Hematology:	<i>Hematocrit, hemoglobin, red blood cell count, white blood cell count, differentials (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, and reticulocytes</i>
Serum chemistry:	<i>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</i>
Urinalysis:	<i>Color, specific gravity, pH, glucose, ketones, protein, bilirubin, urobilinogen, blood. Microscopy will be performed only on urine samples with abnormal urinalysis results.</i>
Coagulation:	<i>Prothrombin time, international normalized ratio, and activated partial thromboplastin time</i>
For WOCBP:	<i>Serum pregnancy test: betaHCG Urine pregnancy test: betaHCG (tested locally at site)</i>

8.12 Blood Sampling for Pharmacokinetics (PK)

Blood samples will be collected to determine the plasma concentrations of nalbuphine and its metabolites. Samples will be collected at the site with safety labs, according to the schedule of events. Further details of PK sample collection and processing will be provided in the laboratory manual. Once processed, samples will be stored for an interim period at the site, before shipping to the central lab for forwarding to the PK lab. Samples that are sent to the PK lab can be stored for up to 5 years in case of the need for retesting for this study before being destroyed.

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

8.13 WOCBP Pregnancy test, and contraceptive counselling

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

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

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

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

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

- Hormonal birth control for at least 3 months prior to baseline – oral, intravaginal, transdermal, injectable, or implantable,
- Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS) in place for at least 1 month prior to baseline visit,
- Bilateral tubal occlusion (e.g. via clipping, ligation, or hysteroscopic occlusion) following confirmation of full occlusion),
- Vasectomized partner,
- Barrier method –
 - male or female condom with or without spermicide;
 - cap, diaphragm or sponge with spermicide,
- Sexual abstinence - Subjects utilizing sexual abstinence as birth control must be counseled on the requirement to use appropriate contraception should they become sexually active. This counseling should occur at each study visit and must be documented in source records.

There are no contraceptive requirements for males.

8.14 Diffusing capacity of the lungs for carbon monoxide (DLCO)

DLCO to measure the carbon monoxide in exhaled air after holding the breath for 10 seconds will be performed with a locally provided device. DLCO testing will be used to assess lung function for the purposes of inclusion in the study.

If the subject has had DLCO assessment in the 12 weeks prior to screening, these results can be used, and the test does not need to be repeated for the purposes of the study.

8.15 Spirometry – Forced Vital Capacity (FVC)

Spirometry will be performed locally at site with a locally provided device, to assess FVC. Performance of spirometry should adhere to ATS/ERS guidelines ([Graham et al, 2019](#)) with reference to predicted equations (predicted values) used locally at the site.

8.16 24-Hour Digital Cough Monitor

Measurement of cough frequency will be done using objective digital cough monitoring, the VitaloJAK[®]. The digital cough monitor consists of a portable sound recording device, which is worn in a pouch or pocket. The small microphone is clipped onto the subject's collar or lapel, as close as possible to the anterior neck, and a sensor is attached to the chest. The device has the capability to make a continuous sound recording of up to 36 hours. The device will be programmed to stop recording automatically after 24-hrs. The recording is encrypted on the device and transferred electronically to the United Kingdom (UK) via a secure web portal. The digital recording is then processed through accompanying computer software, which removes non-cough sounds, automatically registers sound patterns typical for cough, and provides a compressed file for further analysis.

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

At the timepoints defined in the Schedule of Events, site staff will place the digital cough monitor on the subject prior to their departure from the clinic. The monitor will be worn until the following day to obtain at least a full 24-hour recording period of cough frequency. At the end of each recording session, the monitor will be removed at home by the subject prior to bedtime. The monitor will be shipped back to site for upload of data to the vendor portal.

- On Day 1 of the study, the cough monitor will be removed prior to taking the first dose of investigational product.
- For Week 2, the cough monitor will be applied on Day 13, and removed on Day 14 prior to the evening dose.

8.17 Patient Reported Outcome (PRO) Questionnaires

Refer to PRO SoE ([Table 2](#)) for the overall frequency of PRO questionnaires. The questionnaires will be presented to the subject at the appropriate time as a task within the e-diary provided for the purpose of the study. The details on the PROs selected are provided in [Table 9](#).

Table 9 Patient Reported Outcome (PRO) Tools

PRO Abbreviation	PRO Full Title	Nr of Qs	Recall Period
EXACT®	EXAcerbation of Chronic pulmonary disease Tool (The E-RS:IPF respiratory symptom subscales used in the study consists of a subset of 11 items from the EXACT)	14	24 hrs
CS-NRS	Cough Severity Numerical Rating Scale	1	24 hrs
L-IPF® Impacts	Living with Pulmonary Fibrosis Impacts Questionnaire	20	7 days
L-IPF® Symptoms	Living with Pulmonary Fibrosis Symptoms Questionnaire	20	24 hrs
LCQ®	Leicester Cough Questionnaire	19	2 weeks
EQ-5D-5L™	EQ-5D-5L	6	24 hrs
PGI-S Cough PGI-S IPF	Patient Global Impression of Severity – Cough Patient Global Impression of Severity – IPF	2	7 days
PGI-C Cough PGI-C IPF	Patient Global Impression of Change – Cough Patient Global Impression of Change – IPF	2	7 days
SOWS	Subjective Opiate Withdrawal Scale (See Section 8.17.1)	16	24 hrs

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

At Baseline, PROs will be completed prior to the intake of the first dose of IP.

During the study, the EXACT will be completed daily. Other PROs will be completed at post-baseline timepoints the day after the per protocol visit date, regardless of when the actual visit is performed.

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

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

8.17.1 SOWS (Subjective Opiate Withdrawal Scale)

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

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

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

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

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

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

8.19 Randomization

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

8.20 Telephone Contacts

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

- Open ended questions about
 - changes to Concomitant Medication and Therapies
(See [Section 8.6 Concomitant Medication and Therapy Assessments](#))
 - changes to, or new Adverse Events
(See [Section 7 Adverse Events and Serious Adverse Events](#))
- Open ended questions about well-being, and a discussion on managing any concerns around titration symptoms
(See [Section 8.22 Tolerance and Titration Symptoms Management](#))
- Confirm IP intake and compliance
(see [Section 6.4 Subject Compliance and Accountability](#))
- Discussion on e-diary and PRO completion compliance, after review of the portal, as needed (see [Section 8.17 Patient Reported Outcome \(PRO\) Questionnaires](#)).

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

8.21 Study Drug Dispensing and Compliance Management

Refer to [Section 6 Study Treatment](#) of this protocol, and the pharmacy manual for details on the investigational product and its management for the study.

8.22 Tolerance and Titration Symptoms Management

Systematic reviews of the literature found about 22% of patients with non-cancer pain management discontinue opioid therapy because of side effects ([McNichol, 2007](#)). A similar

AE-related discontinuation rate was observed in clinical study TR12. The most frequent titration period related AEs reported with NAL ER are nausea, headache, and dizziness.

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

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

1. **Education and expectations** – balanced information about titration side effects should be provided. Patient material is provided to support with educating about starting NAL ER. Key points for education are:
 - There is a chance that they will experience the side effects, but also a chance they may not have any side effects during titration.
 - If they do experience side effects, there may be ways to manage these.
 - For many individuals, the side effects are transient in nature.
2. **Non-medical management of Titration Symptoms** – A description of the non-medical options to manage side effects is provided in the patient material and includes recommendations like taking the medication together with a meal or snack, ginger, peppermint, and/or travel sickness acupressure bands.
3. **Medications to manage titration symptoms** – The management options in common opioid-induced adverse effects have been reviewed ([Swegle and Logemann, 2006](#)). One source noted that nausea was the most common opioid-related AE that patients want to avoid ([Rogers et al, 2013](#)). The prophylactic treatment and management of established opioid-induced nausea and vomiting has also been reviewed ([Smith et al, 2012](#)).

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

Nausea:

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

Dizziness (and associated nausea if applicable):

- Antihistamines
- Antimuscarinics

Medications that should NOT be used: serotonin 5-HT₃ receptor antagonist (ondansetron/Zofran[®]) - association with serotonin syndrome.

4. **Step down to once daily (QD) dosing:** Up to and including Week 3, if the subject is experiencing intolerable titration side effects, the subject may switch to QD dosing (i.e., skip the morning dose, and take the nighttime dose only) for 1-3 days. After the symptoms have subsided, or at the latest after 3 days, the subject is to restart BID dosing for at least 2 days. The subject can repeat the step down up to 3 times in total if symptoms return. After Week 3, the subject should have resumed consistent BID dosing, unless discussed with the Medical Monitor.

If the above steps have been tried and intolerable symptoms continue, Investigators are strongly encouraged to contact the Medical Monitor for further discussion prior to prematurely discontinuing treatment (see [Section 8.23 Premature Discontinuation / Removal of Subjects from the Trial or Study Drug](#) for additional details). In all cases, the Medical Monitor must be notified within 24 hours of premature discontinuation of treatment.

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

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

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

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

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

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

- 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 occurring after discontinuation and vital status.

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

8.24 Appropriateness of Measurements

The primary efficacy and safety assessments selected were standard for clinical research in this subject population.

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

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

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

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

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Summary statistics will be presented by treatment group. For continuous variables, unless otherwise stated, the number of available observations (n), mean, standard deviation, median, and range will be provided. For continuous variables directly related to cough frequency (24-hour cough frequency, sleeping cough frequency, awake cough frequency), geometric mean and geometric coefficient of variation (CV) will also be presented.

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

9.2 Intercurrent Event Handling

9.2.1 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. This best reflects the clinical concern of interest in the study, which is to examine the difference in 24-hour cough count between NAL ER and placebo subjects, as it treats all subjects as continuing assigned treatment if possible.

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). This approach reflects clinical interests by examining possible real-world usage (e.g., with rescue medication as needed) while not taking a hypothetical approach of assuming subjects will never use rescue medication.

9.2.2 Other 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. The rationale for this strategy is the same as for the primary and key secondary endpoints.

“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. This approach reflects clinical interests by examining possible real-world usage; since these endpoints do not reflect the key clinical concern of the study, it was decided that it was not of clinical usefulness to extrapolate what may have occurred if subjects did not continue treatment if possible.

“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.

9.3 Missing Data

Primary endpoint and key secondary endpoint data will be imputed in the case of permanent treatment discontinuation, as specified in [Section 9.2 Intercurrent Event Handling](#). Primary and key secondary endpoint data that are missing will be similarly imputed if all subsequent primary/key secondary endpoint and dosing/treatment data for that subject are missing but will be unimputed if subsequent data are non-missing. For example, if a subject has non-missing cough frequency at Week 2 and Week 6, but Week 4 is missing for reasons not related to an intercurrent event, Week 4 will be left missing. If Week 2 is present, but Weeks 4 and 6 are missing and treatment/dosing information is missing from Weeks 4 onward, the Week 4 and 6 data will be imputed for the primary and key secondary analyses. Imputation will only take place if a subject has at least one non-missing baseline and one non-missing post-baseline measurement for the endpoint in question.

9.4 Determination of Sample Size

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, and are slightly conservative in comparison to a previous study of Nalbuphine ER in 24-hour cough frequency (data on file).

A total of approximately 160 subjects will be randomized to account for a potential 30% dropout rate.

See [Section 9.13 Interim Analysis](#) for details on the sample size re-estimation.

9.5 Analysis Populations

At a minimum, the following populations will be defined:

- **Modified Intent-to-Treat (mITT) population:** 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 and key secondary endpoint analyses at minimum.
- **Safety population:** The Safety population will consist of all subjects who have received at least one dose of study drug or placebo. Safety subjects will be analyzed according to the treatment taken; if multiple are taken, Safety subjects will be analyzed according to the highest dosage of study drug taken. This population will be used for, at minimum, analyses and summaries of adverse events, vital signs, and laboratory results.

- Pharmacokinetic (PK) population: The PK population will consist of all subjects with at least one evaluable pharmacokinetic sample. This population will be used for any summaries and analyses of PK data.
- Per Protocol (PP) population: The PP population will consist of all subjects in the mITT population who have a treatment compliance >80% during the fixed dose period and do not have a protocol deviation that excludes subjects from the PP population. A complete list of protocol deviations that will exclude subjects from the PP population will be provided in the SAP. Subjects who are withdrawn from the study by the sponsor due to a deviation (see [Section 10.9 Protocol Violations/Deviations](#)) will be excluded from the PP population.

9.6 Demographics and Baseline Characteristics

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

9.7 Subject Disposition

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

9.8 Concomitant Medication

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

9.8.1 Prohibited and Restricted Medications

A separate summary of concomitant medications by ATC of WHO drug, preferred term, and treatment arm will be performed only for prohibited and restricted medications (Table 7). Furthermore, a summary will provide the number of subjects in each treatment arm that took at least one prohibited/restricted concomitant medication, and the summary statistics for total duration of prohibited/restricted medication use. Total duration of prohibited/restricted concomitant medication use will be calculated by summing the period(s) of time in which a subject was taking at least one such medication from first administration of study medication to end of study, based on treatment start/end dates. 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.

9.9 Efficacy Analyses

9.9.1 Primary Efficacy Endpoint

The primary efficacy analysis will be a 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. Missing data will be handled according to the principles in [Section 9.2 Intercurrent Event Handling](#) and [Section 9.3 Missing Data](#).

Since there are 3 comparisons being made (for each active dosage against placebo), Type I error will be controlled using a hierarchical testing procedure. One dosage will be compared to placebo at $\alpha = 0.05$; if this comparison is significant, then a second dosage will be compared to placebo at $\alpha = 0.05$. If the first comparison is non-significant, then no further comparisons will take place. If the second comparison is non-significant, the third dosage will likewise not be compared to placebo. This will maintain a family-wise error rate of 5%. The order in which dosages will be compared to placebo will be specified in the SAP.

As there is a planned sample size re-estimate interim analysis (see [Section 9.13 Interim Analysis](#)), methods will be used to combine the primary endpoint estimates from prior and subsequent to the interim analysis in order to avoid estimation bias ([Cui, Hung, and Wang, 1999](#)). The SAP will contain the specifics the approach used.

9.9.2 Secondary Efficacy Endpoints

The key secondary efficacy analysis will be an MMRM of relative change from baseline in the E-RS:IPF Cough subscale (i.e., EXACT question 2), 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 antifibrotic treatment (y/n) will be included as covariates in the model. Treatment comparisons will be carried out in a hierarchical manner, in the same order as the primary endpoint.

The Baseline will be defined as the mean of 7 days of scores utilizing scores from the 7 days immediately preceding Randomization (Days -8 to -2). 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). Missing data rules will be specified in the statistical analysis plan.

Secondary endpoints related to change in cough frequency (24-hour, awake, or sleep at Weeks 2, 4, and 6) will be modeled using the same MMRM for the primary endpoint with log-transformed responses. No multiplicity adjustments or hierarchical testing will be performed for these endpoints.

Comparison in proportion of 24-hour cough frequency responders ($\geq 30\%$, $\geq 50\%$, and $\geq 75\%$ reduction from baseline) and E-RS:IPF Cough subscale responders (one category improvement) will be compared using a logistic regression with the same fixed effects and covariates as the primary analysis of covariance (ANCOVA).

Secondary analyses of E-RS:IPF Cough subscale score at Weeks 2 and 4 will use the same model as above for Week 6, without hierarchical testing for control of multiplicity.

All analyses of the EXACT questionnaire items (including EXACT question 2) will be performed utilizing methodology for the derivative scale, Evaluating Respiratory Symptoms in IPF, the E-RS:IPF, including the IPF-Breathlessness, IPF-Cough, IPF-Sputum, and IPF-Chest Symptoms subscales, which was designed for use in the IPF population rather than in the chronic obstructive pulmonary disease (COPD) population for which the EXACT was designed.

Other secondary endpoints (e.g., CS-NRS score) will be compared against placebo for each dosage using simple two-sample t-tests or, when appropriate, chi-square or Wilcoxon signed-rank tests. Results will not be adjusted for multiplicity and will be taken as exploratory.

9.10 Safety Analyses

All on-treatment safety data will be assessed descriptively for AEs, SAEs, clinical laboratory measurements, vital signs, spirometry, physical examinations and SOWS. ECG data will be presented in listings and analyzed in a separate report by the ECG specialist vendor. The totality of these data addresses the secondary objective of characterizing the overall safety and tolerability of NAL ER in subjects with IPF. The characterization of safety will also include AEs associated with the known risks of opiate use (e.g., neurologic, respiratory, cardiovascular and GI). Key parameters within the overall descriptive assessment of safety and tolerability are considered to be the incidence of subjects having an SAE (Safety) and subjects discontinuing due to AEs (Tolerability).

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

9.10.1 Adverse Events

All Treatment Emergent AEs (TEAE) will be summarized overall and for each body system and preferred term by treatment group, relationship to investigational product, and severity. For tabulations by severity, only a subject's most severe event within the category (e.g., overall, body system, or preferred term) will be counted. AEs will be dichotomized into "related" (definitely, probably, and possibly) and "unrelated" (unlikely and not related). "Treatment-emergent" will be defined as starting or worsening after the first dose of investigational product. If the start date is missing, the event is assumed to be treatment-emergent. All SAEs will be tabulated separately, as well as AEs leading to discontinuation.

As part of a formal investigation of a drug that is classified as CNS active drug within the opioid drug class, certain adverse events will be documented in more detail to support an eight-factor analysis. See [Section 7.2.2 Adverse Events Requiring Additional Narratives](#) for the list of applicable adverse events.

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

9.10.2 Clinical Laboratory Assessments

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

9.10.3 Vital Signs

Vital signs, including blood pressure, heart rate, body temperature, respiration rate, SpO₂, and weight will be summarized by treatment group at baseline and at each scheduled visit.

9.10.4 Spirometry

FVC will be summarized by treatment group at baseline and at each scheduled visit.

9.10.5 Physical Examinations

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

9.10.6 Subjective Opiate Withdrawal Scale (SOWS)

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

9.10.7 Electrocardiograms

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

9.11 Pharmacokinetics (PK) and Pharmacodynamics (PD) Analysis

The study drug plasma concentration data will be provided as data listings and will be summarized by nalbuphine dose, collection time relative to dose and/or relative to ECG where applicable.

Ad-hoc pharmacokinetic analyses will be conducted through population, and may be detailed in the SAP.

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

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

Further details, including PK-PD modeling, may be detailed in the SAP.

9.12 Other Assessment or Analysis

To explore the dose-response relationship, the relationship between the log-transformed relative change in hourly 24-hour cough frequency will be modeled against dosage using a 4-parameter sigmoidal Hill dose-response curve. The exact specifications of this model will be described in the SAP. Furthermore, the dose-response will be plotted against the response both on the log scale as fitted and on the back-transformed scale in terms of % change in 24-hour

cough frequency from baseline. These plots will include 90% 2-sided confidence and prediction limits.

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

9.13 Interim Analysis

When approximately 50% of the subjects have either completed the Week 6 measurements or have discontinued/become lost to follow-up, a sample size re-estimation (SSRE) will be performed. Using the methods of *Mehta and Pocock (2011)*, an unblinded statistician will calculate the conditional power of the 108mg arm as compared to the placebo arm for the primary endpoint. If the conditional power is below 80% and within a pre-specified “promising zone”, the statistician will provide a recommendation to increase the study sample size (up to a maximum total sample size of 400). While only the 108mg and placebo arms are being compared, the sample sizes of all 4 arms will be increased in order to maintain equal information for each treatment/dosage. If the conditional power falls below a pre-specified futility boundary, the statistician will provide a non-binding recommendation to stop the study early for futility; there will not be a penalty or study change if this recommendation is discarded and the study continues. 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). The specifics of this SSRE, including specification of the promising zone and futility boundaries, will be provided in the DSMB SAP.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Quality Control and Assurance

The Sponsor shall implement and maintain quality control and quality assurance procedures with written Standard Operating Procedures (SOP) to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), 2018, CTR EU 536/2014*, and equivalent regulatory body regulations/guidelines as applicable.

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

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

10.2 Investigators and Study Administrative Structure

The following will be maintained in the TMF:

- List of the CRO, laboratories, medical or technical vendors
- List of DSMB members (in the DSMB charter).
- Coordinating Investigators designated by country, as required by local regulations, and defined in the relevant Clinical Trial Application (CTA).
- List of Principal Investigators, clinical study sites, and the relevant departments.

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

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

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

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

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

10.4 Ethical Conduct of the Study

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

10.5 Patient Information and Consent

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

10.6 Patient Confidentiality and Data Protection

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

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

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

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

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

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

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

10.7 Study Monitoring

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

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

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

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

10.8 Case Report Forms and Study Records

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

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

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

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

10.9 Protocol Violations/Deviations

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Deviations may or may not result in the sponsor making a decision to have the subject withdrawn from the study and/or render that subject ineligible for inclusion in the Per Protocol population. The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

10.10 Access to Source Documentation

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

- Signed ICFs for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/IEC
- Composition of the IRB/IEC or other applicable statement
- Record of all communications between the Investigator and Sponsor (or CRO)
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study and their signatures
- Copies of eCRFs and of documentation of corrections for all subjects
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH - Essential Documents for the Conduct of a Clinical Trial, *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), 2018*

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

10.11 Data Generation and Analysis

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

- Objective digital cough monitor (VitaloJAK)
- Patient Reported Outcome (PRO) questionnaires
- Clinical Global Impression assessments
- Nalbuphine plasma concentrations

- For safety the objective: adverse events, clinical lab tests, vital signs, pulse oximetry, physical examinations, and spirometry.

All subject data generated on site for the study will be documented in source records maintained by the site, and no data is recorded in the eCRF directly. Data will be recorded on eCRFs. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

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

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

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

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

10.12 Retention of Data

When the study is completed, the Investigator must retain the essential documents for 25 years to comply with regulatory guidelines before destroying the data. The Investigator will notify the Sponsor prior to moving or destroying any of the study documents. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. The Investigator should take measures to prevent any accidental or premature destruction of these documents.

10.13 Financial Disclosure

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

10.14 Publication and Disclosure Policy

The Sponsor will retain ownership of all data. When the study is complete, the Sponsor will arrange the analysis and tabulation of data. A clinical study report will then be prepared, which

may be used for publication, presentation at scientific meetings, or submission to regulatory authorities. The results of the study will be posted to the publicly available website ClinicalTrials.gov independent of the outcome of the study. All proposed publications based on this study will be subject to the Sponsor's approval requirements.

11 REFERENCE LIST

- Ai, Q., Hu, Y., Wang, Y. J., Wu, S. X., Qin, Z., Wang, J., Wang, G. L., Zhang, J. Y., An, M. H. (2010). Pentazocine pretreatment suppresses fentanyl-induced cough. *Pharmacological Reports*, 62, 747-750. doi.org/10.1016/S1734-1140(10)70333-9
- Bacci, E. D., O'Quinn, S., Leidy, N. K., Murray, L., Vernon, M. (2018). Evaluation of a respiratory symptom diary for clinical studies of idiopathic pulmonary fibrosis. *Respiratory Medicine*, 134, 130-138. doi.org/10.1016/j.rmed.2017.11.011
- Bacci, E. D., O'Quinn, S., Leidy, N. K., Murray, L., Vernon, M. (2018). Evaluation of a respiratory symptom diary for clinical studies of idiopathic pulmonary fibrosis. *Respiratory Medicine*, 134, 130-138. Online supplement. doi.org/10.1016/j.rmed.2017.11.011
- Boulet, L. P., Coeytaux, R. R., McCrory, D. C., French, C. T., Chang, A. B., Birring, S. S., Smith, J., Diekemper, R. L., Rubin, B., Irwin, R. S. (2015). Tools for Assessing Outcomes in Studies of Chronic Cough. CHEST Guideline and Expert Panel Report *CHEST*, 147(3), 804-814. doi.org/10.1378/chest.14-2506
- Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)*. 2007;4(7):28-37.w
- Canning, B. J., Chang, A. B., Bolser, D. C., Smith, J. A., Mazzone, S. B., McGarvey, L. (2014). Anatomy and Neurophysiology of Cough. CHEST Guideline and Expert Panel Report. *CHEST*, 146(6), 1633-1648. doi.org/10.1378/chest.14-1481
- Center for Disease Control and Prevention. (2016). CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *Morbidity and Mortality Weekly Report*, 65(1). cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?s_cid=rr6501e1_w
- Cheng, X. Y., Lun, X. Q., Li, H. B., Zhang, Z. J. (2016). Butorphanol suppresses fentanyl-induced cough during general anesthesia induction. A randomized, double-blinded, placebo-controlled clinical trial. *Medicine*, 95(26), e3911. dx.doi.org/10.1097/MD.00000000000003911
- Clinical Trials Facilitation and Coordination Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials (Version 1.1, CTFG 21/09/2020)
- Clinical trials - Regulation EU No 536/2014. European Commission Public Health. https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en
- Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. United States Department of Health and Human Services. (2017, November 27)
- Credible Meds®, Resources for Healthcare Professionals, QTc Drugs List, crediblemeds.org. Updated April 6, 2023. Accessed on August 7, 2023
- Cui, L., Hung, H. M. J., & Wang, S. J. (1999). Modification of Sample Size in Group Sequential Clinical Trials. *Biometrics*, 55(3), 853-857. doi.org/10.1111/j.0006-341X.1999.00853.x

- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1). Guidance for Industry. United States Department of Health and Human Services. (2018, March). <https://www.fda.gov/media/93884/download>
- Gal, T. J., DiFazio, C. A., & Moscicki, J. (1982). Analgesic and Respiratory Depressant Activity of Nalbuphine: A Comparison with Morphine. *Anesthesiology*, 57(5), 367-374. doi.org/10.1097/00000542-198211000-00004
- Guy, W. ECDEU Assessment Manual for Psychopharmacology (Revised, 1976) Biometric Laboratory, The George Washington University, Kensington, MD. National Institute of Mental Health, Rockville, MD.
- Graham, B. L., Steenbruggen, I., Miller, M. R., Barjaktarevic, I. Z., Cooper, B. G., Hall, G. L., Hallstrand, T. S., Kaminsky, D. A., McCarthy, K., McCormack, M. C., Oropez, C. E., Rosenfeld, M., Stanojevic, S., Swanney, M. P., & Thompson, B. R. (2019). Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *American Journal of Respiratory and Critical Care Medicine*, 200(8), e70-e88. <https://doi.org/10.1164/rccm.201908-1590ST>
- Hope-Gill, B. D. M., Hilddrup, S., Davies, C., Newton, R. P., Harrison, N. K. (2003). A Study of the Cough reflex in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine*, 168, 995-1002. doi.org/10.1164/rccm.200304-597OC
- Jennings, A. L., Davies, A. N., Higgins, J. P. T., Gibbs, J. S. R., Broadley, K. E. (2002). A systematic review of the use of opioids in the management of dyspnoea. *Thorax*, 57, 939-944. doi.org/10.1136/thorax.57.11.939
- Klepper, I. D., Rosen, M., Vickers, M. D., & Mapleson, W. W. (1986). Respiratory Function Following Nalbuphine and Morphine in Anaesthetized Man. *British Journal of Anaesthesia*, 58, 625-629. doi.org/10.1093/bja/58.6.625
- Krajnik, M., Jassem, E., Sobanski, P. (2014). Opioid receptor bronchial tree: current science. *Current Opinion in Supportive and Palliative Care*, 8, 191-199. doi.org/10.1097/SPC.0000000000000072
- Lederer, D. J., Martinez, F. J. (2018). Idiopathic Pulmonary Fibrosis. *The New England Journal of Medicine*, 378(19), 1811-1823. doi.org/10.1056/NEJMra1705751
- Ley, B., Collard, H. R., King Jr., T. E. (2011). Concise Clinical Review: Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. *American Journal of Respiratory and Critical Care Medicine*, 183, 431-440. doi.org/10.1164/rccm.201006-0894CI
- List of Psychotropic Substances under International Control (In accordance with the Convention of Psychotropic Substances of 1971). United Nations Publication. 33rd edition, 2022. International Narcotics Control Board. Green List.
- Mehta, C. R., Pocock, S. J.. (2011), Adaptive increase in sample size when interim results are promising: A practical guide with examples. *Statistics in Medicine*, 30 (28) p.3267-3284. DOI: 10.1002/sim.4102

- Mahler, D. A. (2013). Opioids for refractory dyspnea. *Expert Review of Respiratory Medicine*, 7(2), 123-135. doi.org/10.1586/ers.13.5
- Mahler, D. A., O'Donnell, D. E. (2015). Recent Advances in Dyspnea. *CHEST*, 147(1), 232-241. doi.org/10.1378/chest.14-0800
- Mazzone, S. B., McGovern, A. E., Koo, K., Farrell, M. J. (2009). Mapping supramedullary pathways involved in cough using functional brain imaging: Comparison with pain. *Pulmonary Pharmacology & Therapeutics*, 22, 90-96. doi.org/10.1016/j.pupt.2008.08.003
- McNichol, E. (2007). Opioid Side Effects. *PAIN Clinical Updates*, 15(2). doi.org/10.1016/j.jaip.2019.04.012
- Medicines Evaluation Board Netherlands. (2010, August 23). PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands. Nalbuphine HCl Orpha solution for injection 10 mg/ml Orpha-Devel Handels und Vertriebs GmbH, Austria. nalbuphine (as hydrochloride) db.cbg-meb.nl/pars/h30852.pdf
- Morice, A. H., Menon, M. S., Mulrennan, S. A., Everett, C. F., Wright, C., Jackson, J., Thompson, R. (2007). Opiate Therapy in Chronic Cough. *American Journal of Respiratory and Critical Care Medicine*, 175, 312-315. doi.org/10.1164/rccm.200607-892OC
- Morice, A. H., Millqvist, E., Bieksiene, K., Birring, S. S., Dicpinigaitis, P., Ribas, C. D., Boon, M. H., Kantar, A., Lai, K., McGarvey, L., Rigau, D., Satia, I., Smith, J., Song, W. J., Tonia, T., van den Berg, W. K., van Manen, M. J. G., Zacharasiewicz, A. (2020). ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *European Respiratory Journal*, 55, 19011136. doi.org/10.1183/13993003.01136-2019
- Nalpain® Nalbuphine for injection. Summary of Product Characteristics. January 2011. United Kingdom.
- National Opioid Use Guideline Group (Canada). (2010, April 30). Canadian Guideline For Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. Part B: Recommendations for Practice. nationalpaincentre.mcmaster.ca/opioid/
- Nubain Public Assessment Report. June 18, 2020. Altamedics GmbH. DE/H/6001/001/DC
- Nubain U.S. Prescribing Information. 2023. Par Pharmaceutical.
- Parshall, M. B., Schwartzstein, R. M., Adams, L., Banzett, R. B., Manning, H. L., Borbeau, J., Calverley, P. M., Gift, A. G., Harver, A., Lareau, S. C., Mahler, D. A., Meek, P. A., O'Donnell, D. E. (2012). An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. *American Journal of Respiratory and Critical Care Medicine*, 185(4), 435-452. doi.org/10.1164/rccm.201111-2042ST
- Pugh, G. C., Brown, D. T., & Drummond, G. B. (1989). Effect Of Nalbuphine Hydrochloride on The Ventilatory and Occlusion Pressure Responses to Carbon Dioxide in Volunteers. *British Journal of Anaesthesia*, 62(6), 601-609. doi.org/10.1093/bja/62.6.601

- Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J. Brown, K. K., Colby, T. V., Cordier, J., Flaherty, K. R., Lasky, J. A., Lynch, D. A., Ryu, J. H., Swigris, J. J., Wells, A. U., Ancochea, J., Bouros, D., Carvalho, C., Costabel, U., Ebina, M., Hansell, D. M. et al. (2011). An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *American Journal of Respiratory and Critical Care Medicine*, 183, 788-824. doi.org/10.1164/rccm.2009-040GL
- Raghu, G., Richeldi, L. (2017). Current approaches to the management of idiopathic pulmonary fibrosis. *Respiratory Medicine*, 129, 24-30. dx.doi.org/10.1016/j.rmed.2017.05.017
- Raghu, G., Remy-Jardin, M., Myers, J. L., Richeldi, L., Ryerson, C. J., Lederer, D. J., Behr, J., Cottin, V., Danoff, S. K., Morell, F., Flaherty, K. R., Wells, A., Martinez, F. J., Azuma, A., Bice, T. J., Bouros, D., Brown, K. K., Collard, H. R., Duggal, Abhijit, Galvin, L., Inoue, Y., et al. (2018). Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*, 198(5), e44-e68. dx.doi.org/10.1164/rccm.201807-1255ST
- Raghu, G., Remy-Jardin, M., Richeldi, L., Thomson, C. C., Inoue, Y., Johkoh, T., Kreuter, M., Lynch, D. A., Maher, T. M., Martinez, F. J., Molina-Molina, M., Myers, J. L., Nicholson, A. G., Ryerson, C. J., Strek, M. E., Troy, L. K., Wijsenbeek, M., Mammen, M. J., Hossain, T., Bissell, B. D. (2022). Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine*, 205(9), e18-e47. dx.doi.org/10.1164/rccm.202202-0399ST
- Ramirez, J. M., Burgraff, N. J., Wei, A. D., Baertsch, N. A., Varga, A. G., Baghdoyan, H. A., Lydic, R., Morris, K. F., Bolser, D. C., & Levitt, E. S. (2021). Neuronal mechanisms underlying opioid-induced respiratory depression: our current understanding. *Journal of Neurophysiology*, 125(5), 1899-1919. doi.org/10.1152/jn.00017.2021
- Rogers E, Mehta S, Shengelia R, Reid MC. Four Strategies for Managing Opioid-Induced Side Effects in Older Adults. *Clin Geriatr*. 2013;21(4)
- Romagnoli, A. & Keats, A. S. (1978). Comparative Hemodynamic Effects of Nalbuphine and Morphine in Patients With Coronary Artery Disease. *Cardiovascular Diseases*, 5(1), 19-24. Pubmed Central PMCID: PMC287700
- Romagnoli, A., & Keats, A. S. (1980). Ceiling effect for respiratory depression by nalbuphine. *Clinical Pharmacology & Therapeutics*, 27(4), 478-485. doi.org/10.1038/clpt.1980.67
- Smith HS, Smith JM, Seidner P. Opioid-induced nausea and vomiting. *Ann Palliat Med*. 2012;1(2):121-129. doi:10.3978/j.issn.2224-5820.2012.07.08
- Swegle JM, Logemann C. Management of common opioid-induced adverse effects. *Am Fam Physician*. 2006;74(8):1347-1354.

- Swigris, J. J., Stewart, A. L., Gould, M. K., Wilson, S. R. (2005). Patients' perspectives on how idiopathic pulmonary fibrosis affects the quality of their lives. *Health and quality of Life Outcomes*, 61(3). doi.org/10.1186/1477-7525-3-61
- Swigris, J. J., Fairclough, D. L., Morrison, M., Make, B., Kozora, E., Brown, K. K., Wamboldt, F. S. (2011). Benefits of Pulmonary Rehabilitation in Idiopathic Pulmonary Fibrosis. *Respiratory Care*, 56(6), 783-789. doi.org/10.4187/respcare.00939
- The Voice of the Patient. A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative. Idiopathic Pulmonary Fibrosis. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. (2015). fda.gov/files/about%20fda/published/The-Voice-of-the-Patient--Idiopathic-Pulmonary-Fibrosis.pdf
- Torbutrol® (butorphanol tartrate) veterinary injection and tablets [United States package insert]. Kalamazoo, MI: Zoetis Inc.; 2013.
- United States Drug Enforcement Agency, Office of Diversion Control, Drug & Chemical Evaluation Section. Nalbuphine Hydrochloride. January 2023
- United States Department of Justice. (2023, April). Lists of: Scheduling Actions Controlled Substances Regulated Chemicals. Drug Enforcement Agency, Diversion Control Division, Drug and Chemical Evaluation Section. <https://www.deadiversion.usdoj.gov/schedules/orangebook/orangebook.pdf>
- Volkow, N. D., McLellan, A. T. (2016). Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies. *The New England Journal of Medicine*, 374(13), 1253-1263. doi.org/10.1056/NEJMr1507771
- Wang, J., Duan, J., Wang, Q., Lu, Y. (2020). Pretreatment with Nalbuphine Prevents Sufentanil-Induced Cough During the Anesthesia Induction: A Randomized Controlled Trial. *Therapeutics and Clinical Risk Management*, 16, 281-286. doi.org/10.2147/TCRM.S247437
- Wang, J., Duan, J., Wang, Q., Lu, Y. (2023). Pretreatment with Nalbuphine Prevents Sufentanil-Induced Cough During the Anesthesia Induction: A Randomized Controlled Trial. *Therapeutics and Clinical Risk Management*, 16, 281-286. doi.org/10.2147/TCRM.S247437
- Yaksh, T. L., Wallace, M. S. (2011). Opioids, Analgesia, and Pain Management. In B. A. Chabner, L. L. Brunton, B. C. Knollmann. *Goodman and Gilman's Pharmacological Basis of Therapeutics*. (pp. 481-526). McGraw-Hill Professional.
- Yorke, J., Spencer, L. J., Duck, A., Ratcliffe, S., Kwong, G. N., Longshaw, M. S., Belkin, A., Swigris, J. J. (2014). Cross-Atlantic modification and validation of the A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF-cA). *BMJ Open Respiratory Research*, 1, e000024. doi:10.1136/bmjresp-2014-000024
- Zebraski, S. E., Kochenash, S. M., Raffa, R. B. (2000). MINIREVIEW Lung Opioid Receptors: Pharmacology and Possible Target for Nebulized Morphine in Dyspnea. *Life Sciences*, 66(23), 2221-2231. doi.org/10.1016/S0024-3205(00)00434-3

APPENDICES

LIST OF APPENDICES

Appendix 1	Sponsor Signature	81
Appendix 2	Investigator’s Signature.....	82
Appendix 3	IPF Diagnosis Guidelines ATS/ERS/JRS/ALAT IPF	83

Appendix 1 Sponsor Signature

Study 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)

Short Study Title Cough Reduction in IPF with nalbuphine ER (CORAL)

Study Number: NAL03-202

Protocol Version **Protocol Amendment 2: 20-May-2024**

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

_____, MD

Trevi Therapeutics Inc.

DocuSigned by:

Signer Name: _____
Signing Reason: I approve this document
Signing Time: 20-May-2024 | 2:21 PM EDT
7A861C5E53044F92933590205F8920E6

Signature and Date:

Appendix 2 Investigator's Signature

Study 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)

Short Study Title Cough Reduction in IPF with nalbuphine ER (CORAL)

Study Number: NAL03-202

Protocol Version **Protocol Amendment 2: 20-May-2024**

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

Name and Credentials _____

Job Title _____

Affiliation _____

Signature and Date _____

Appendix 3 **IPF Diagnosis Guidelines ATS/ERS/JRS/ALAT IPF**

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

③ Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY, EUROPEAN RESPIRATORY SOCIETY, JAPANESE RESPIRATORY SOCIETY, AND ASOCIACIÓN LATINOAMERICANA DE TÓRAX FEBRUARY 2022

Abstract

Background: This American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax guideline updates prior idiopathic pulmonary fibrosis (IPF) guidelines and addresses the progression of pulmonary fibrosis in patients with interstitial lung diseases (ILDs) other than IPF.

Methods: A committee was composed of multidisciplinary experts in ILD, methodologists, and patient representatives. 1) Update of IPF: Radiological and histopathological criteria for IPF were updated by consensus. Questions about transbronchial lung cryobiopsy, genomic classifier testing, antacid medication, and antireflux surgery were informed by systematic reviews and answered with evidence-based recommendations using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. 2) Progressive pulmonary fibrosis (PPF): PPF was defined, and then radiological and physiological criteria for PPF were determined by consensus. Questions about pirfenidone and nintedanib were informed by systematic reviews and answered

with evidence-based recommendations using the GRADE approach.

Results: 1) Update of IPF: A conditional recommendation was made to regard transbronchial lung cryobiopsy as an acceptable alternative to surgical lung biopsy in centers with appropriate expertise. No recommendation was made for or against genomic classifier testing. Conditional recommendations were made against antacid medication and antireflux surgery for the treatment of IPF. 2) PPF: PPF was defined as at least two of three criteria (worsening symptoms, radiological progression, and physiological progression) occurring within the past year with no alternative explanation in a patient with an ILD other than IPF. A conditional recommendation was made for nintedanib, and additional research into pirfenidone was recommended.

Conclusions: The conditional recommendations in this guideline are intended to provide the basis for rational, informed decisions by clinicians.

Keywords: idiopathic pulmonary fibrosis; progressive pulmonary fibrosis; radiology; histopathology

③ You may print one copy of this document at no charge. However, if you require more than one copy, you must place a reprint order. Domestic reprint orders: amy.schraver@sheridan.com; international reprint orders: louisa.mott@springer.com.

Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022
Copyright © 2022 by the American Thoracic Society
DOI: 10.1164/rccm.202202-0399ST
Internet address: www.atsjournals.org

Contents

Introduction
Methods
Part I: Update on Diagnosis and Treatment of IPF
Radiological Features of UIP
Histopathological Features of UIP
Evidence-based Recommendations for Diagnosis of IPF
Diagnostic Approach

Evidence-based Recommendations for Treatment of IPF
Management Approach
Future Directions
Part II: Diagnosis and Treatment of PPF in Fibrotic ILD, Other than IPF
Definition of PPF
Physiological Criteria for PPF
Radiological Criteria for PPF

Evidence-based Recommendations for Treatment of PPF, Other than IPF
Future Directions
Conclusions

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial pneumonia of unknown cause that is associated with radiological and histologic features of usual interstitial pneumonia (UIP). It occurs primarily in older adults, is characterized by progressive worsening of dyspnea and lung function, and has a poor prognosis. Diagnosis and management of IPF were addressed in prior guidelines (1–3). A formal American Thoracic Society (ATS) and European Respiratory Society (ERS) proposal process determined that several topics from the previous guidelines warrant reassessment, including the following: radiological and histopathological features of UIP, diagnostic criteria, diagnostic and treatment approaches, and prior evidence-based recommendations about antacid medications and transbronchial lung cryobiopsy (TBLC). In addition, it was decided that new questions about antireflux surgery and genomic classifier testing should be addressed.

The acceptance of antifibrotic therapies for IPF led to the investigation of such

therapies in other fibrotic lung diseases. While the IPF guidelines were being updated, a clinical trial reporting a beneficial effect of antifibrotic medication in interstitial lung diseases (ILDs) other than IPF that manifest progressive pulmonary fibrosis (PPF) was published (4, 5), prompting a paradigm shift toward an en bloc approach to antifibrotic therapy. Given the importance and timeliness of the issue, the guideline committee was approved to expand its scope to also define progression of pulmonary fibrosis and to decide whether the en bloc approach to antifibrotic therapy should continue, or whether therapy should be restricted to specific types of progressive ILD.

These guidelines for the diagnosis and treatment of IPF and other types of PPF are the result of a collaboration among the ATS, ERS, Japanese Respiratory Society (JRS), and Asociação Latinoamericana de Tórax (ALAT). They are intended to provide the basis for rational, informed decisions. The recommendations should never be considered absolute requirements by anyone who evaluates the actions of a healthcare professional.

Methods

Methods including conflict-of-interest management were established *a priori* and are described in the online supplement. The document can be conceptualized in two parts. Narrative portions (e.g., radiological criteria, histopathological criteria, physiological criteria, definitions) were created using consensus by discussion. Guideline portions address specific questions related to TBLC, genomic classifier testing, antacid medication, antireflux surgery for IPF, and pirfenidone and nintedanib for PPF. These sections are compliant with the Institute of Medicine standards for trustworthy guidelines (6) and yield recommendations that were informed by systematic reviews and were formulated and graded using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (7) (Table 1).

Evidence-based recommendations were formulated by discussion followed by voting. Briefly, committee members were provided the following options: a strong recommendation for a course of action, a

ORCID IDs: 0000-0001-7506-6643 (G.R.); 0000-0003-1944-4288 (M.R.-J.); 0000-0001-8594-1448 (L.R.); 0000-0002-5861-0683 (C.C.T.); 0000-0003-3994-874X (Y.I.); 0000-0003-1237-2349 (T.J.); 0000-0003-4402-2159 (M.K.); 0000-0002-6329-2325 (D.A.L.); 0000-0001-7192-9149 (T.M.M.); 0000-0002-2412-3182 (F.J.M.); 0000-0002-1852-1723 (M.M.-M.); 0000-0001-8247-3028 (J.L.M.); 0000-0002-7671-1023 (M.E.S.); 0000-0002-7426-336X (L.K.T.); 0000-0002-4527-6962 (M.W.); 0000-0003-0343-3234 (M.J.M.); 0000-0002-1995-7828 (T.H.); 0000-0002-7345-9731 (B.D.B.); 0000-0002-0390-8407 (S.M.H.); 0000-0002-5434-9342 (Y.H.K.); 0000-0002-5352-9587 (M.M.); 0000-0002-2825-506X (I.B.-R.); 0000-0003-2484-1923 (F.C.); 0000-0002-2961-3455 (B.C.); 0000-0002-5368-0412 (A.L.O.); 0000-0002-9559-1485 (A.P.); 0000-0002-1022-4783 (M.S.); 0000-0002-4404-3833 (S.L.K.); 0000-0003-4328-6822 (M.G.); 0000-0003-4429-2263 (K.C.W.).

Supported by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociação Latinoamericana de Tórax.

An Executive Summary of this document is available at <http://www.atsjournals.org/doi/suppl/10.1164/rccm.202202-0399ST>.

Correspondence and requests for reprints should be addressed to Ganesh Raghu, M.D., 1959 NE Pacific Avenue, University of Washington Medical Center-Montlake Campus, Center for Interstitial Lung Diseases, Medical Specialty Clinics (3rd floor), Box 356175, Seattle, WA 98195. E-mail: graghu@uw.edu.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

conditional recommendation for a course of action, a conditional recommendation against a course of action, a strong recommendation against a course of action, and abstention (Table 2). Abstention was appropriate whenever a committee member was unwilling to commit for or against the proposed course of action, such as when there was insufficient evidence, or the committee member had insufficient expertise or a self-realized bias. Three outcomes were possible:

1. Greater than 20% abstentions indicated that there was an insufficient quorum for decision making. If the primary reason for the abstentions was insufficient evidence, a research recommendation was also made.
2. Fewer than 20% abstentions with >70% agreement on the appropriate course of action yielded a graded recommendation. This result was indicated by a statement beginning "We recommend ..." for strong recommendations or "We suggest ..." for conditional recommendations.
3. Fewer than 20% abstentions with >70% agreement on the appropriate course of action yielded no recommendation because of insufficient agreement among the committee members regarding the appropriate course of action. This result was indicated by the statement, "We make no recommendation for or against ... because of insufficient agreement among the committee members."

Table 1. Summary of Methods

Methods	Used
Conflict-of-interest disclosure, vetting, and management prespecified	Y
Guideline committee multidisciplinary	Y
Guideline committee has patient representation	Y
Literature search strategy prespecified	Y
Multiple databases searched for relevant studies	Y
Titles and abstracts screened in duplicate	Y
Study selection criteria prespecified	Y
Study selection and data extraction performed in duplicate	Y
Studies aggregated by meta-analysis when possible	Y
GRADE approach used to formulate recommendations	Y
GRADE approach used to rate the strength of recommendation and quality of evidence	Y
Public commentary period	N
Process exists to periodically reassess for updating	Y

Definition of abbreviations: GRADE = Grading of Recommendations, Assessment, Development and Evaluation; N = no; Y = yes.

Part I: Update on Diagnosis and Treatment of IPF

Radiological Features of UIP

Radiological features of UIP, the hallmark of IPF, were described in detail in the 2018 guidelines for diagnosis of IPF (2). The guideline committee concluded that several radiological features warrant reiteration in the current guideline for emphasis, and they reconsidered the categories of high-resolution computed tomography (HRCT) patterns.

Spectrum of HRCT findings in IPF.

Lung fibrosis is confidently recognized when traction bronchiectasis/bronchiolectasis (Figure 1) and/or honeycombing (Figure 2) are identified, although honeycombing must be distinguished from paraseptal emphysema (Figure 3) and airspace enlargement with fibrosis (Figure 4). Pathologic-computed tomography correlations have demonstrated that honeycombing and traction bronchiolectasis are closely related. Honeycombing corresponds to bronchiolar cysts, developed after collapse of fibrotic alveolar septa and dilatation of terminal airways (8, 9). The cystic structures sometimes can be followed throughout the lobular core and seem to be connected with each other and are in continuity with the bronchial tree (10). Honeycombing cysts consist of both dilatation of peripheral airspaces due to surrounding alveolar septal fibrosis and tangentially viewed traction bronchiolectasis (11). HRCT findings typical of UIP and honeycombing on HRCT correlate best with bronchiolectasis

histologically (12). Recent observations have underlined that in IPF, the remodeling process appears to be a continuum from traction bronchiectasis to honeycombing and that conceptual separation of the two processes may be misleading (13). Identification of traction bronchiectasis/bronchiolectasis and honeycombing on computed tomography (CT) scans is associated with moderate interobserver agreement (14–16).

The UIP pattern is a hallmark of IPF (IPF-UIP), but it can also be seen in patients with fibrotic hypersensitivity pneumonitis (HP) (Figure 5), connective tissue disease (CTD) (CTD-UIP) (Figure 6), or exposure-related ILDs. HP-UIP and CTD-UIP may sometimes be suspected on the basis of imaging appearance but are often indistinguishable radiologically from IPF-UIP. Pleuroparenchymal fibroelastosis may be seen in 6–10% of cases of IPF (17, 18) (Figure 7); it may be associated with more rapid decline in lung function, higher risk of pneumothorax and pneumomediastinum, and poorer survival (17).

Probable UIP pattern in the diagnostic approach to IPF. Four HRCT categories were defined in the 2018 guidelines for diagnosis of IPF: UIP pattern, probable UIP pattern, indeterminate for UIP pattern, and alternative diagnosis (2) (Figures 1, 2, 4, and 8). Merger of the UIP and probable UIP patterns into a single category was considered; however, the guideline committee decided to retain the four categories with minor modifications for the purpose of clarity (Table 3).

There were several reasons that merging the UIP and probable UIP categories was considered: 1) there is increasing evidence that patients with the probable UIP pattern and UIP pattern on HRCT have similar disease behavior and clinical courses (19–21); 2) the likelihood of histologic confirmation of UIP in patients with the probable UIP pattern ranges from 80% to 85% (19, 22, 23); and 3) in the appropriate clinical context, histopathological confirmation of the UIP pattern is not required to ascertain the diagnosis of IPF in patients with either the probable UIP pattern or the UIP pattern (2, 24, 25).

Despite these reasons, the guideline committee opted to maintain the differentiation between the two patterns for several reasons: 1) studies describing the correlation of probable UIP with

Table 2. Implications of the Guideline Recommendations

	Strong Recommendation ("We Recommend ...")	Conditional Recommendation ("We Suggest ...")
From the GRADE working group		
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action, and only a small minority would not.	The majority of individuals in this situation would want the suggested course of action, but a sizable minority would not.
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for different patients, and you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
For policy makers	The recommendation can be adapted as policy in most situations, including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary among regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.
Additional conceptualization from the ATS/ERS/JRS/ALAT Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis Guidelines panel discussion		
	It is the right course of action for .95% of patients. "Just do it."	It is the right course of action for .50% of patients. "Slow down, think about it, discuss it with the patient."
	You would be willing to tell a colleague who did not follow the recommendation that he/she did the wrong thing.	You would not be willing to tell a colleague who did not follow the recommendation that he/she did the wrong thing; it is "style" or "equipoise."
	The recommended course of action may be an appropriate performance measure.	The recommended course of action is not appropriate for a performance measure.

Definition of abbreviations: ALAT = Asociaci3n Latinoamericana de T3rax; ATS = American Thoracic Society; ERS = European Respiratory Society; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; JRS = Japanese Respiratory Society. Adapted from Reference 7.

histopathological UIP are from expert settings, and correlation in alternative settings is unknown; 2) there is evidence suggesting that patients with probable UIP might have better survival (19, 26); 3) the predictive value of the probable UIP CT pattern for histologic UIP is slightly lower than for the UIP CT pattern, suggesting that the probable UIP CT pattern may show more overlap with other fibrotic lung diseases such as fibrotic HP; and 4) there is evidence that the predictive value of a probable UIP pattern for histologic UIP is lower in individuals with relatively mild

fibrosis and in younger individuals (27). Although the UIP pattern and probable UIP pattern remain separate (Figure 9), the diagnostic approaches for these entities are similar (Figure 10), and histologic confirmation is usually unnecessary unless there is clinical concern for an alternative diagnosis (25).

Histopathological Features of UIP

The histopathological criteria that characterize UIP and probable UIP were reviewed and confirmed. A diagnosis of UIP made by biopsy is predicated on a

combination of the following: 1) patchy dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing); 2) a predilection for subpleural and paraseptal lung parenchyma; 3) fibroblast foci; and 4) the absence of features that suggest an alternative diagnosis (2). When all of these features are present, a UIP pattern can be established with confidence. "Probable UIP" refers to biopsies in which some of these findings are present in the absence of features to suggest an alternative diagnosis.

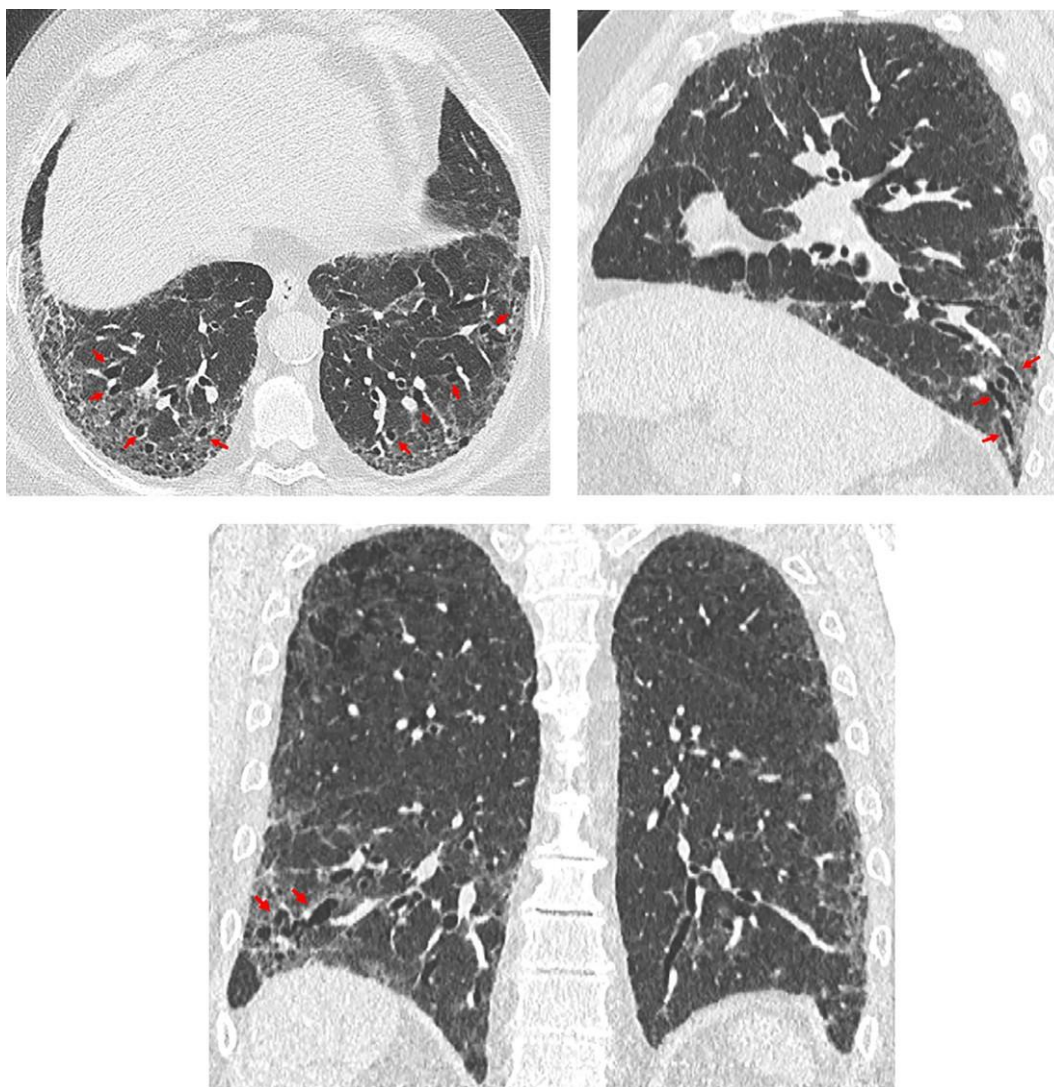


Figure 1. Traction bronchiectasis/bronchiolectasis. Axial, sagittal, and coronal computed tomography images show subpleural-predominant, lower lung-predominant reticular abnormality with traction bronchiectasis (arrows). Traction bronchiectasis/bronchiolectasis represents irregular bronchial and/or bronchiolar dilatation caused by surrounding retractile fibrosis; distorted airways are thus identified in a background of reticulation and/or ground-glass attenuation. On contiguous high-resolution computed tomography sections, the dilated bronchi or bronchioles can be tracked back toward more central bronchi. The pattern in this patient represents the probable usual interstitial pneumonia pattern.

The committee concluded that the evolving use of TBLC merits commentary. Application of the histopathological criteria for UIP is more challenging with TBLC specimens because 1) the subpleural predominance of pathologic changes may not be readily appreciated and 2) the potential for sampling error results in less confident exclusion of features that may suggest an alternative diagnosis. Compared with surgical lung biopsy (SLB), TBLC is more likely to demonstrate a probable UIP pattern than a definite UIP pattern given the limited sampling of subpleural lung parenchyma in most cases (28). Nevertheless,

a combination of patchy fibrosis, fibroblast foci, and the absence of features to suggest an alternative diagnosis is usually sufficient to establish a probable UIP pattern on TBLC (29). Combining UIP and probable UIP patterns in the context of multidisciplinary discussion (MDD) results in comparable rates of diagnostic agreement for SLB and TBLC in patients with IPF (28).

Evidence-based Recommendations for Diagnosis of IPF

We suggest that TBLC be regarded as an acceptable alternative to SLB for making a histopathological diagnosis in patients with

ILD of undetermined type in medical centers with experience performing and interpreting TBLC (conditional recommendation, very low quality evidence).

Background. The 2018 guidelines for diagnosis of IPF addressed TBLC in patients with ILD of undetermined type but failed to garner enough agreement to make a consensus recommendation for or against TBLC (2). Additional studies have been published since the previous guideline; therefore, the guideline committee decided to reconsider the evidence pertaining to TBLC. In contrast, the 2018 diagnosis of IPF

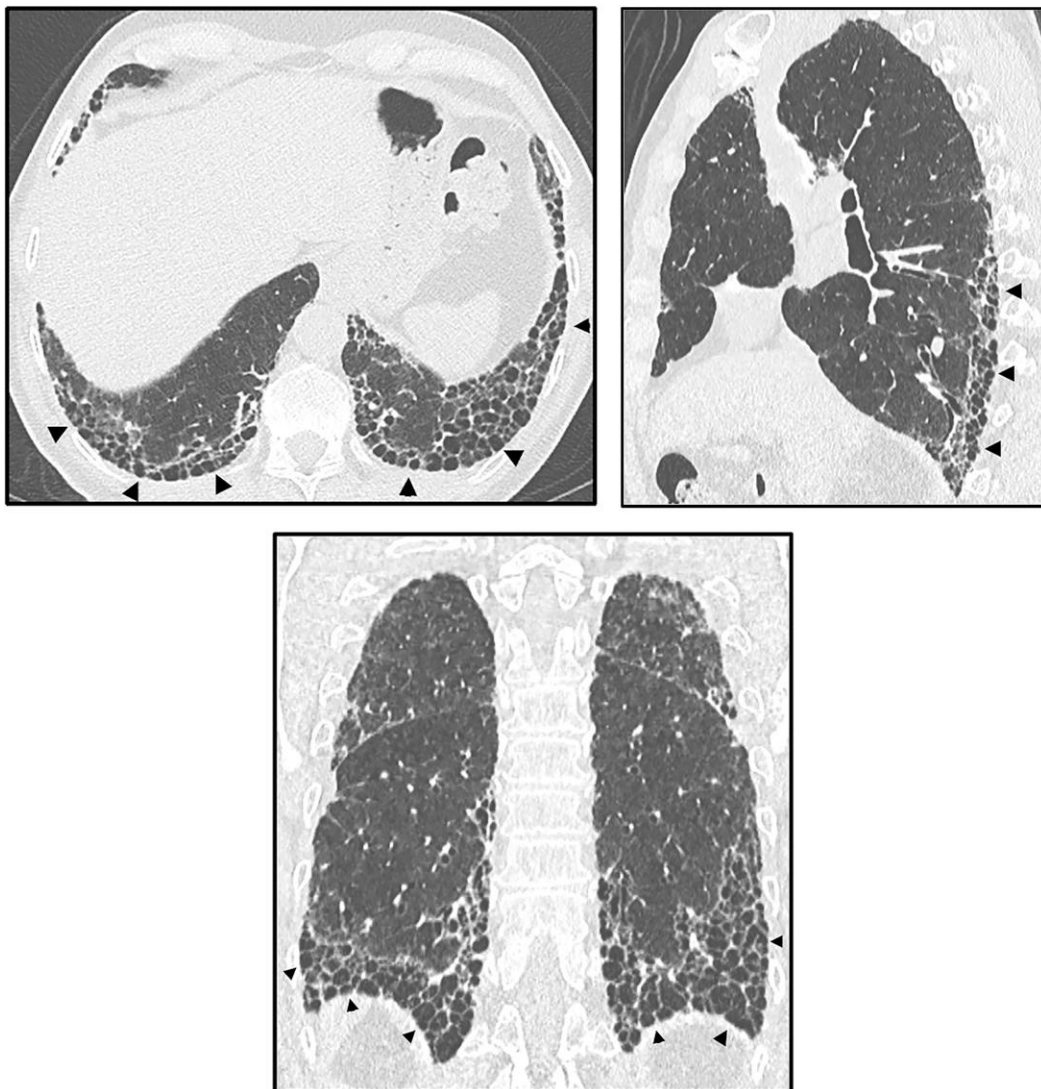


Figure 2. Honeycombing. Axial, sagittal, and coronal computed tomography images show subpleural-predominant, lower lung-predominant reticular abnormality with honeycombing (arrowheads). Honeycombing is defined by clustered, thick-walled, cystic spaces of similar diameters, measuring between 3 and 10 mm but up to 2.5 cm in size. The size and number of cysts often increase as the disease progresses. Often described in the literature as being layered, a single layer of subpleural cysts is also a manifestation of honeycombing. Honeycombing is an essential computed tomography criterion for typical (“definite”) usual interstitial pneumonia–idiopathic pulmonary fibrosis pattern when seen with a basal and peripheral predominance. In this pattern, honeycombing is usually associated with traction bronchiolectasis and a varying degree of ground-glass attenuation.

guidelines’ recommendation pertaining to SLB was not reevaluated (2). The committee concluded that there is insufficient new evidence to warrant reconsideration of the SLB recommendation at this time; in addition, a separate ERS task force may soon be addressing the topic.

Summary of evidence. The committee asked, “Should patients with newly detected ILD of undetermined type who are clinically suspected of having IPF undergo TBLC to obtain samples to make a histopathological diagnosis?” The systematic review that

informed the committee’s recommendation is being published independently (30); we summarize the salient findings. Diagnostic yield was designated as a critical outcome. The remaining outcomes were rated as important outcomes, including diagnostic agreement and various complications.

The systematic review identified 40 studies that evaluated TBLC in patients with ILD of undetermined type (28, 31–69). The studies ranged in size from 12 to 699 patients and used either a 1.9- or 2.4-mm cryoprobe with fluoroscopic guidance. Five of the

studies were prospective (28, 32, 48, 60, 69), most used deep sedation, most used rigid bronchoscopy, and the number and location of samples varied widely across studies.

Regarding selection of diagnostic yield rather than sensitivity and specificity as the critical outcome, diagnostic yield is appropriate if the intervention is the reference standard, but sensitivity and specificity are appropriate if the intervention is compared with a reference standard. In this case, histopathological diagnosis was chosen *a priori* as the reference standard,

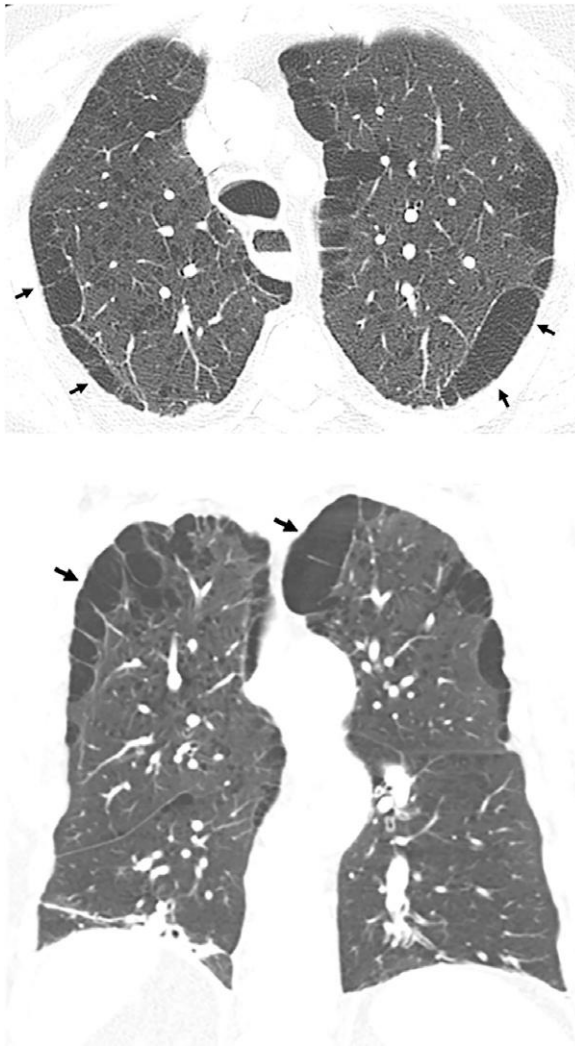


Figure 3. Paraseptal emphysema. Axial and coronal computed tomography images show relatively large subpleural cysts of paraseptal emphysema (arrows), mainly in the upper lobes. Centrilobular emphysema is also present. The subpleural cysts of paraseptal emphysema usually occur in a single layer and are larger than honeycomb cysts (typically > 1 cm); they are not associated with other features of fibrosis such as reticular abnormality or traction bronchiectasis.

making diagnostic yield the appropriate outcome. Clinical, radiological, and histopathological criteria applied by MDD were not chosen as the reference standard, because this would likely lead to misleading overestimates of sensitivity and specificity because of “incorporation bias.”

Incorporation bias occurs when the test results are a component of the reference standard; in this case, histopathology obtained by TBLC is a key component of the diagnostic criteria considered during MDD.

DIAGNOSTIC YIELD. Diagnostic yield was defined as the number of procedures

that yielded a histopathological diagnosis divided by the total number of procedures performed. The diagnostic yield of TBLC in patients with ILD of undetermined type was 79% (28, 31–38, 40, 41, 44–47, 50–52, 54, 55, 57, 58, 60–63, 65, 66, 68). There was no difference in diagnostic yield across subgroups related to publication date, study size, or cryoprobe size. Only sample number appeared to affect diagnostic yield, with a diagnostic yield of 85% when three or more samples were collected (28, 33, 38, 44, 45, 51, 55, 63, 66, 69) and a diagnostic yield of 77% or less when fewer samples were collected.

DIAGNOSTIC AGREEMENT. Two studies reported agreement between the diagnostic interpretation of TBLC samples and SLB samples (28, 60). The larger study demonstrated 70.8% agreement, which increased to 76.9% diagnostic agreement after MDD (28). *Post hoc* analysis suggested that agreement of TBLC with SLB improves by taking more samples (29). In contrast, the smaller study reported diagnostic agreement of only 38% (60).

COMPLICATIONS. Complications of TBLC included pneumothorax in 9% (28, 31, 33–35, 37, 39–43, 46, 48–50, 53–55, 60, 63, 68, 69) and any bleeding in 30% (28, 31, 33, 36, 39, 47, 50, 51, 55, 67–69). Severe bleeding, procedural mortality, exacerbations, respiratory infections, and persistent air leak were rare.

QUALITY OF EVIDENCE. The quality of evidence was very low for all outcomes, meaning that the committee should have very low confidence in the estimated effects, and therefore, the effects should be interpreted with caution. The main reason for the very low quality rating was that most of the studies were uncontrolled case series, and many were limited by not enrolling consecutive patients (potential selection bias).

Guideline committee conclusions. The original question and systematic review involved the comparison of TBLC versus no TBLC (i.e., TBLC followed by SLB, if needed, vs. going directly to SLB). However, the committee concluded that the comparison had become outdated because observations published during guideline development suggest that patients who have nondiagnostic findings on TBLC are likely to also have nondiagnostic findings on SLB. This changed the clinically meaningful comparison to TBLC versus SLB. Therefore, the committee compared the estimated 80% diagnostic yield of TBLC (according to the present systematic review) to the estimated 90% diagnostic yield of SLB (according to a previously published systematic review) (2) and also considered that the sampling techniques provide similar diagnostic confidence in the context of MDD (2). They also compared the 9% and rare risk of pneumothorax and severe bleeding, respectively, on TBLC with the 6% and rare risk of pneumothorax and severe bleeding, respectively, on SLB (2). The committee judged the comparison favorably when one considers that TBLC is less invasive and less costly than SLB. As a result, the committee concluded that TBLC may be considered an



Figure 4. Airspace enlargement with fibrosis (AEF), also called smoking-related interstitial fibrosis, in a cigarette smoker. Axial and sagittal images show clustered asymmetric cysts that are larger and more irregular than typical honeycomb cysts, without traction bronchiectasis or other signs of fibrosis (arrows). Emphysema is also present. AEF is not regarded as a distinct form of idiopathic interstitial pneumonia but results from the presence of a greater amount of fibrosis than usually described in the classic definition of emphysema.

acceptable alternative to SLB in experienced centers that have standardized their protocols to include steps to minimize risk and maximize diagnostic yield, as described in detail elsewhere (70). The committee emphasized the importance of the experience of the person performing the TBLC, the facilities, and the person interpreting the samples in the success of TBLC (as in SLB) and concluded that a conditional recommendation is more appropriate than a strong recommendation

to account for variation in capabilities across institutions.

The committee also emphasized that TBLC may not be appropriate for all patients. Similar physiological criteria should be considered whether assessing a patient's suitability for TBLC or SLB. Severe lung function derangement (e.g., FVC, 50% predicted, DL_{CO} , 35%), moderate or severe pulmonary hypertension (estimated systolic pulmonary arterial pressure ≥ 40 mm Hg), uncorrectable bleeding risk, and/or significant

hypoxemia (PaO_2 , 55–60 mm Hg) are associated with a higher risk of adverse outcomes and are considered relative contraindications (32, 71, 72).

There are emerging data regarding the safety and diagnostic yield of TBLC in subjects in whom SLB would not be performed because of significant lung function impairment or comorbidities. Although there are inconsistencies across studies, the data suggest that TBLC may be a reasonable option in some patients at higher risk for major complications, particularly when performed in higher volume centers. One study of 96 subjects from two centers reported no difference in the rates of adverse outcomes or length of hospitalization in higher risk patients (body mass index ≥ 35 kg/m², age ≥ 75 yr, FVC $\geq 50\%$, DL_{CO} , 30%, systolic pulmonary arterial pressure ≥ 40 mm Hg, or significant cardiac disease) compared with lower risk patients (73). Another study of 699 patients undergoing TBLC reported that both pathological and final multidisciplinary diagnostic yield were lower in patients with significant lung function impairment (FVC $\geq 50\%$ and/or DL_{CO} , 35%). However, there were no significant differences in complications (59). Finally, another study showed that modified Medical Research Council score > 2 , FVC $< 50\%$, and Charlson Comorbidity Index > 2 were factors that predicted early and overall hospital readmission in the following 90 days. The overall mortality in this study at 90 days was 0.78% (32).

Guideline committee vote. The committee's vote was as follows: strong recommendation to consider TBLC an appropriate alternative, 8 of 33 (24%); conditional recommendation to consider TBLC an appropriate alternative, 23 of 33 (70%); conditional recommendation to not consider TBLC an appropriate alternative, 2 of 33 (6%); and strong recommendation to not consider TBLC an appropriate alternative, 0 of 33 (0%). One participant abstained from voting because of insufficient expertise.

Research needs. The evidence was notable for inconsistency across studies, with some groups reporting significantly higher diagnostic yields than others. This suggests the continued need for procedural standardization, with subsequent measurement of outcomes, adjustments, and reevaluation.

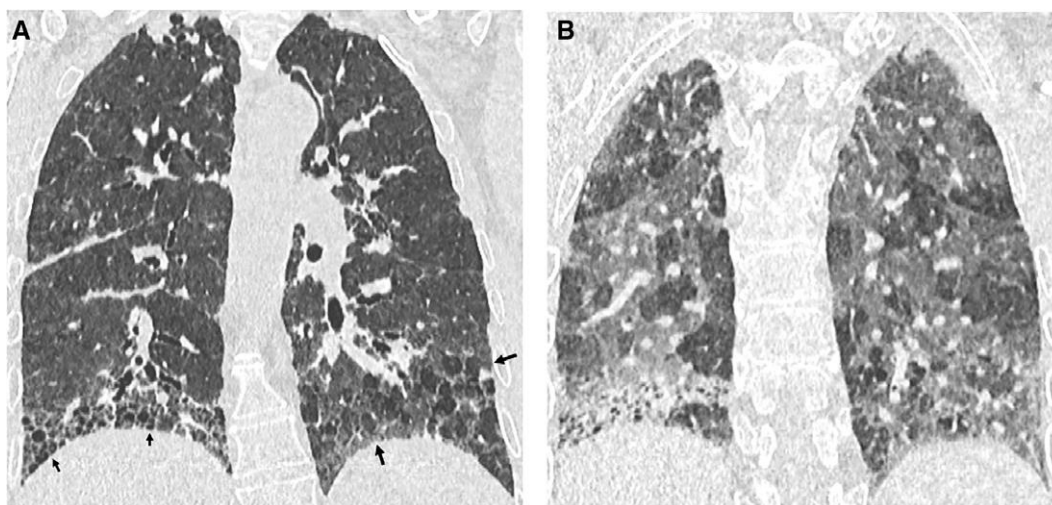


Figure 5. Spectrum of computed tomography (CT) appearances in usual interstitial pneumonia (UIP) pattern due to hypersensitivity pneumonitis (HP). (A) Coronal CT section obtained at deep inspiration showing honeycombing with traction bronchiolectasis in the peripheral part of the right lower lobe (short arrows) and numerous hyperlucent lobules in the left lower lobe (long arrows). (B) Lobular air trapping was confirmed on expiratory CT. HP-UIP should be considered when fibrosis and honeycomb cysts predominate in the upper or mid lungs, when mosaic attenuation or three-density sign is present, or when the fibrosis appears diffuse in the axial plane.

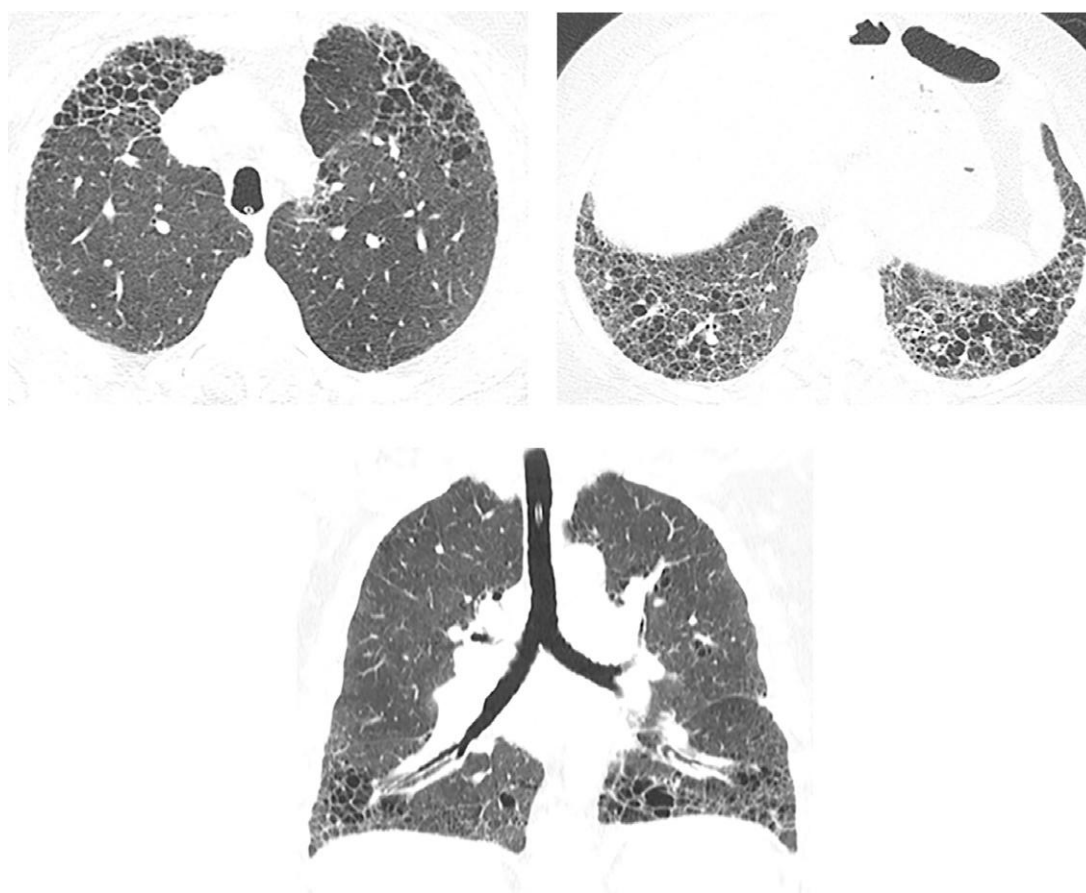


Figure 6. Usual interstitial pneumonia (UIP) pattern due to connective tissue disease (CTD-UIP) in a patient with dermatomyositis/scleroderma overlap. Axial and coronal images show sharply demarcated fibrosis with exuberant honeycombing in the lower lobes and in the anterior upper lobes. CTD-UIP should be considered when honeycomb cysts are extensive, occupying >70% of the fibrotic portions of the lung (exuberant honeycombing sign); when fibrotic abnormality is sharply demarcated on coronal images from the relatively normal upper lungs (straight-edge sign); and when there is relative increase in fibrosis in the anterior upper lobes (anterior upper lobe sign).



Figure 7. Combined pleuroparenchymal fibroelastosis and usual interstitial pneumonia patterns. Coronal computed tomography image shows dense subpleural fibrosis at the lung apices with traction bronchiectasis and upper lobe volume loss. There is subpleural reticular abnormality and honeycombing in both lower lobes.

We make no recommendation for or against the addition of genomic classifier testing for the purpose of diagnosing UIP in patients with ILD of undetermined type who are undergoing transbronchial forceps biopsy, because of insufficient agreement among the committee members.

Background. A genomic classifier was developed with machine learning and whole transcriptome RNA sequencing using lung tissue obtained by SLB. More recently, it was introduced and validated for lung tissue obtained by transbronchial forceps biopsy (74, 75). The appropriateness of genomic classifier testing in patients with ILD of unknown type has never been considered in the context of a clinical practice guideline.

Summary of evidence. The committee asked, “Should genomic classifier testing be performed for the purpose of diagnosing UIP in patients with ILD of undetermined type who are undergoing transbronchial forceps biopsy?” The systematic review that informed the committee’s recommendation is published independently (76); we summarize the salient findings. Diagnostic test characteristics were rated as critical outcomes, while diagnostic agreement, diagnostic confidence, and the adverse consequences of misclassification were rated as important outcomes.

The systematic review identified four relevant studies, which included a total of 195 patients with ILD of unknown type (75, 77–79). All of the studies were accuracy studies. Two of the studies also measured agreement in the categorization of UIP and non-UIP when a genomic classifier was or was not used, as well as diagnostic confidence before and after the use of a genomic classifier (75, 77).

DIAGNOSTIC TEST CHARACTERISTICS. All four studies reported diagnostic test characteristics of genomic classifier testing and were included in a meta-analysis (75, 77–79). The individual studies reported sensitivity ranging from 59% to 80% and specificity ranging from 78% to 100% using histopathological diagnosis from samples obtained by SLB, TBLC, or MDD as the reference standard. When aggregated by meta-analysis, genomic classifier testing identified the UIP pattern with sensitivity and specificity of 68% and 92%, respectively, in patients with ILD of unknown type.

DIAGNOSTIC AGREEMENT AND CONFIDENCE. Two studies reported diagnostic agreement and confidence (75, 77). Multidisciplinary teams evaluated anonymized clinical information, radiology results, and either molecular classifier or histopathology results to categorize patients as having UIP pattern or non-UIP pattern.

The studies then measured agreement of the categorizations obtained with and without genomic classifier testing, as well as diagnostic confidence before and after the use of genomic classifier data. One study reported agreement of 86% between categorical IPF or non-IPF diagnoses made using molecular classifier results or histopathology, with an increase in diagnostic confidence after the incorporation of genomic classifier data (75). The other study reported agreement of 88% between categorical IPF or non-IPF clinical diagnoses made by MDD with and without genomic classifier results, with an increase in the diagnostic confidence when genomic classifier results were considered (77).

QUALITY OF EVIDENCE. The quality of evidence is determined by the critical outcomes, which was rated as low. There were well-done accuracy studies downgraded because of imprecision (wide confidence intervals and few patients), the maker of the diagnostic test funded three of the studies, and several of the individuals who developed the diagnostic test also conducted the studies (i.e., confirmation bias).

Guideline committee conclusions. The guideline committee made no recommendation for or against genomic classifier testing, because of insufficient agreement among the committee members. There were two schools of thought among the committee members. Those who favored genomic classifier testing believed that the high specificity provided important diagnostic information that can be used in MDD and, therefore, may reduce the need for additional sampling for histopathology diagnosis. Those who argued against genomic classifier testing believed that a recommendation in favor of testing was premature because 1) the sensitivity needs to improve (otherwise, a negative result fails to definitively exclude UIP); 2) the downstream consequences of false-negative results need to be better understood; 3) additional studies are necessary to obtain more precise estimates of sensitivity and specificity; 4) existing data incompletely address the incremental diagnostic value conferred by genomic classifier testing beyond what clinical and radiological data already provide, particularly given the possibility of a UIP pattern’s existing in a variety of ILDs; 5) the results do not provide the granular details that histopathology provides and are useful only in the context of MDD; 6) the importance of identifying UIP is less clear in

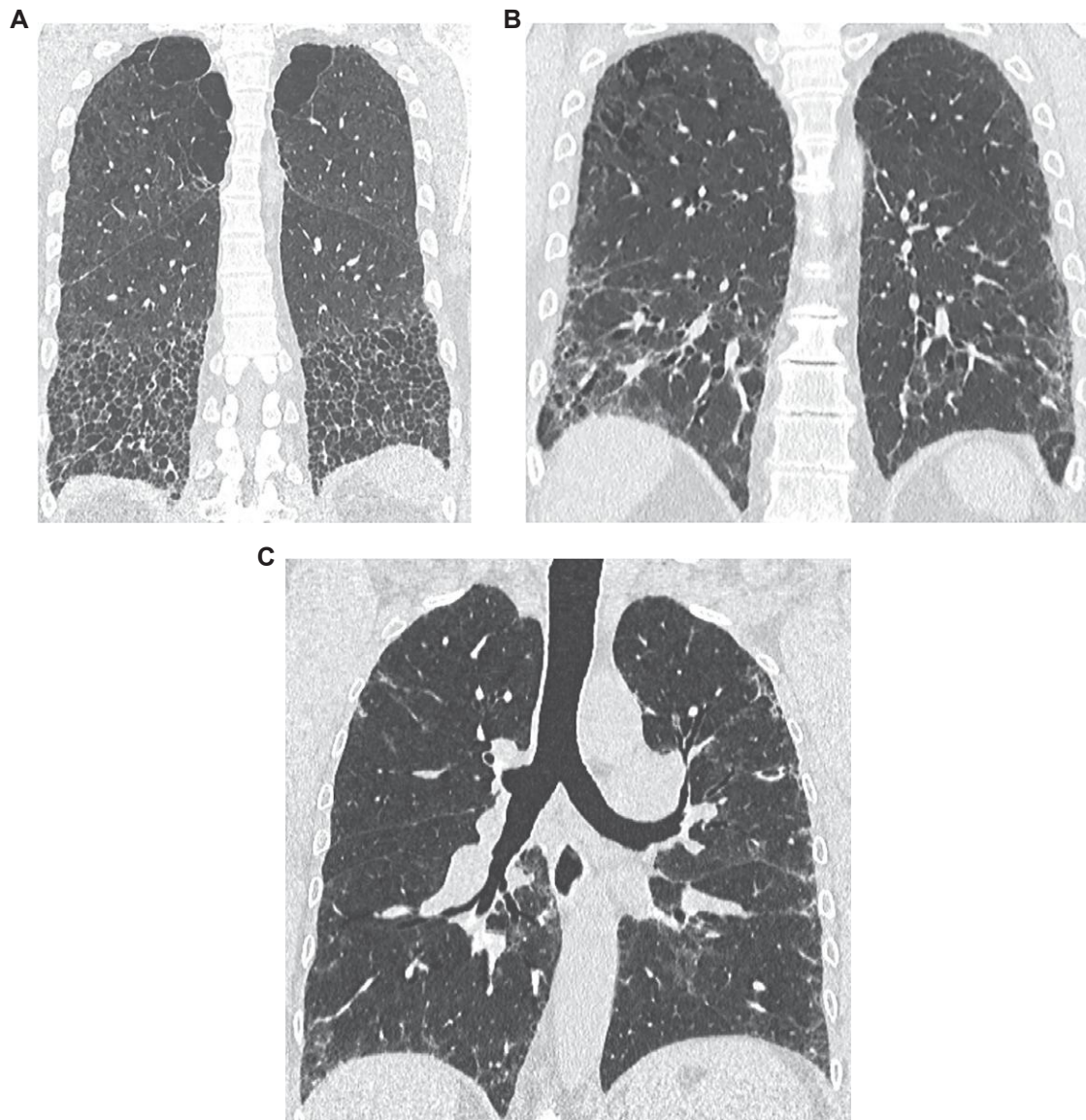


Figure 8. Three of the four high-resolution computed tomography patterns of usual interstitial pneumonia (UIP): (A) UIP pattern (associated with some paraseptal and centrilobular emphysema in the upper lobes), (B) probable UIP pattern with fibrotic features in the lung periphery (and some centrilobular emphysema in the upper lobes), and (C) indeterminate for UIP pattern (peribronchovascular and subpleural ground-glass opacities, intermingled with fine reticulation but no honeycombing or traction bronchiectasis). The fourth category, alternative diagnosis, is widely variable, depending on the specific alternative diagnosis, and is not shown.

the context of expanding antifibrotic indications; and 7) such testing is not yet widely available. Many also believed that transbronchial forceps biopsy testing needs to be considered at the same time that genomic classifier testing is considered because transbronchial forceps biopsy may have complications (the complications of transbronchial lung biopsy were reported in a previous guideline [2]); in other words, the questions are inseparable. There was consensus that genomic classifier testing

should be reconsidered once additional studies are published.

Guideline committee vote. The committee's vote was as follows: strong recommendation for genomic classifier testing, 2 of 34 (6%); conditional recommendation for genomic classifier testing, 12 of 34 (35%); conditional recommendation against genomic classifier testing, 16 of 34 (47%); and strong recommendation against genomic classifier testing, 3 of 34 (12%). One participant

abstained from voting because of insufficient expertise.

Research needs. The evidence base was notable for imprecision (wide confidence intervals) due to the small study sizes. Additional studies are needed to obtain more exact estimates of sensitivity and specificity. Research is also needed to improve the technique's sensitivity, assess the downstream consequences of false-negative results (i.e., incorrectly categorizing a patient with the UIP pattern as not having the UIP

Table 3. High-Resolution Computed Tomography Patterns in Idiopathic Pulmonary Fibrosis

	HRCT Pattern			CT Findings Suggestive of an Alternative Diagnosis
	UIP Pattern	Probable UIP Pattern	Indeterminate for UIP	
Level of confidence for UIP histology	Confident (.90%)	Provisional high confidence (70–89%)	Provisional low confidence (51–69%)	Low to very low confidence (<50%)
Distribution	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with fibrosis) • Occasionally diffuse • May be asymmetric	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/bronchiolectasis)	• Diffuse distribution without subpleural predominance	• Peribronchovascular predominant with subpleural sparing (consider NSIP) • Perilymphatic distribution (consider sarcoidosis) • Upper or mid lung (consider fibrotic HP, CTD-ILD, and sarcoidosis) • Subpleural sparing (consider NSIP or smoking-related IP)
CT features	• Honeycombing with or without traction bronchiectasis/bronchiolectasis • Presence of irregular thickening of interlobular septa • Usually superimposed with a reticular pattern, mild GGO • May have pulmonary ossification	• Reticular pattern with traction bronchiectasis/bronchiolectasis • May have mild GGO • Absence of subpleural sparing	• CT features of lung fibrosis that do not suggest any specific etiology	• Lung findings ◦ Cysts (consider LAM, PLCH, LIP, and DIP) ◦ Mosaic attenuation or three-density sign (consider HP) ◦ Predominant GGO (consider HP, smoking-related disease, drug toxicity, and acute exacerbation of fibrosis) ◦ Profuse centrilobular micronodules (consider HP or smoking-related disease) ◦ Nodules (consider sarcoidosis) ◦ Consolidation (consider organizing pneumonia, etc.) • Mediastinal findings ◦ Pleural plaques (consider asbestosis) ◦ Dilated esophagus (consider CTD)

Definition of abbreviations: CT = computed tomography; CTD = connective tissue disease; DIP = desquamative interstitial pneumonia; GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IP = interstitial pneumonia; LAM = lymphangioleiomyomatosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; PLCH = pulmonary Langerhans cell histiocytosis; UIP = usual interstitial pneumonia. The previous term, "early UIP pattern," has been eliminated to avoid confusion with "interstitial lung abnormalities" described in the text. The term "indeterminate for UIP" has been retained for situations in which the HRCT features do not meet UIP or probable UIP criteria and do not explicitly suggest an alternative diagnosis. Adapted from Reference 2.

IPF suspected*		Histopathology pattern [†]			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely) [‡]	Non-IPF dx
	Indeterminate	IPF	IPF (Likely) [‡]	Indeterminate [§]	Non-IPF dx
	Alternative diagnosis	IPF (Likely) [‡]	Indeterminate [§]	Non-IPF dx	Non-IPF dx

Figure 9. Idiopathic pulmonary fibrosis (IPF) diagnosis on the basis of high-resolution computed tomography (HRCT) and biopsy patterns, developed using consensus by discussion. *"Clinically suspected of having IPF" is defined as unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest computed tomography, bibasilar inspiratory crackles, and age $\geq$ 60 years. Middle-aged adults ($\geq$ 40 and $\leq$ 60 yr old) can rarely present with otherwise similar clinical features, especially in patients with features suggesting familial pulmonary fibrosis. [†]Diagnostic confidence may need to be downgraded if histopathological assessment is based on transbronchial lung cryobiopsy given the smaller biopsy size and greater potential for sampling error compared with surgical lung biopsy. [‡]IPF is the likely diagnosis when any of the following features are present: 1) moderate to severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man $\geq$ 50 years old or in a woman $\geq$ 60 yr old, 2) extensive ($\geq$ 30%) reticulation on HRCT and age $\geq$ 70 yr, 3) increased neutrophils and/or absence of lymphocytosis in BAL fluid, and 4) multidisciplinary discussion produces a confident diagnosis of IPF. [§]Indeterminate for IPF 1) without an adequate biopsy remains indeterminate and 2) with an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation. Adapted from Reference 2. dx = diagnosis; UIP = usual interstitial pneumonia.

pattern), and determine the ability of genomic classifier testing to differentiate UIP related to IPF and UIP related to other types of ILD.

Diagnostic Approach

The committee updated key figures from the 2018 guidelines for diagnosis of IPF (2). The primary change to the diagnostic algorithm is that patients with an HRCT pattern of probable UIP are now managed similarly to patients with UIP, meaning that lung sampling after initial MDD is less likely (Figure 10). The key change to the figure describing combinations of HRCT and histologic patterns is that an HRCT pattern suggestive of an alternative diagnosis combined with a histopathology pattern of probable UIP is now considered indeterminate for IPF rather than non-IPF (Figure 9). The rationale is the committee's observation that patients with this combination of findings can have heterogeneous patterns of disease behavior and outcomes, including sometimes being similar to patients with IPF; therefore, labeling this as "indeterminate" seems preferable to the more limiting guidance that was provided in the previous guideline (2).

Evidence-based Recommendations for Treatment of IPF

We suggest not treating patients with IPF with antacid medication for the purpose of improving respiratory outcomes (conditional recommendation, very low quality evidence). Remarks: Antacid medication and other interventions may be appropriate for patients with both IPF and symptoms of gastroesophageal reflux disease (GERD) for the purpose of improving gastroesophageal reflux (GER)-related outcomes in accordance with GER-specific guidelines.

Background. Antacid medication was suggested in previous guidelines to improve respiratory outcomes in patients with IPF (1, 3). The recommendations were based on several observations. First, up to 90% of patients with IPF have abnormal acidic GER (80, 81). Second, patients with IPF have a high prevalence of hiatal hernias (82). Third, in theory, microaspiration might worsen IPF. Fourth, a retrospective cohort study reported that antacid therapy was associated with a survival benefit in patients with IPF (83). Finally, another observational study found a modest but statistically significant reduction in the FVC decline and fewer acute exacerbations (84). Since those

recommendations were initially formulated, new evidence has been published, so the guideline committee revisited the topic.

Summary of evidence. The committee asked, "Should patients with IPF and confirmed GER, with or without symptoms of GERD, be treated with antacid medications to improve respiratory outcomes?" The systematic review that informed the committee's recommendation is published independently (85); we summarize the salient findings. Five outcomes were designated as critical: disease progression, mortality, exacerbations, hospitalizations, and lung function. Two outcomes were designated as important: GER severity and adverse effects.

An initial scoping review identified no studies that specifically analyzed patients with IPF who were stratified as either having or not having confirmed GER to determine the efficacy of antacid medication in these subgroups. Therefore, the search strategy and study selection criteria were broadened, and indirect evidence was sought (i.e., studies that enrolled patients with IPF regardless of whether GER had been confirmed). Fifteen studies were identified that evaluated antacid medication in patients with IPF. The number of participants ranged from 20 to 3,704.

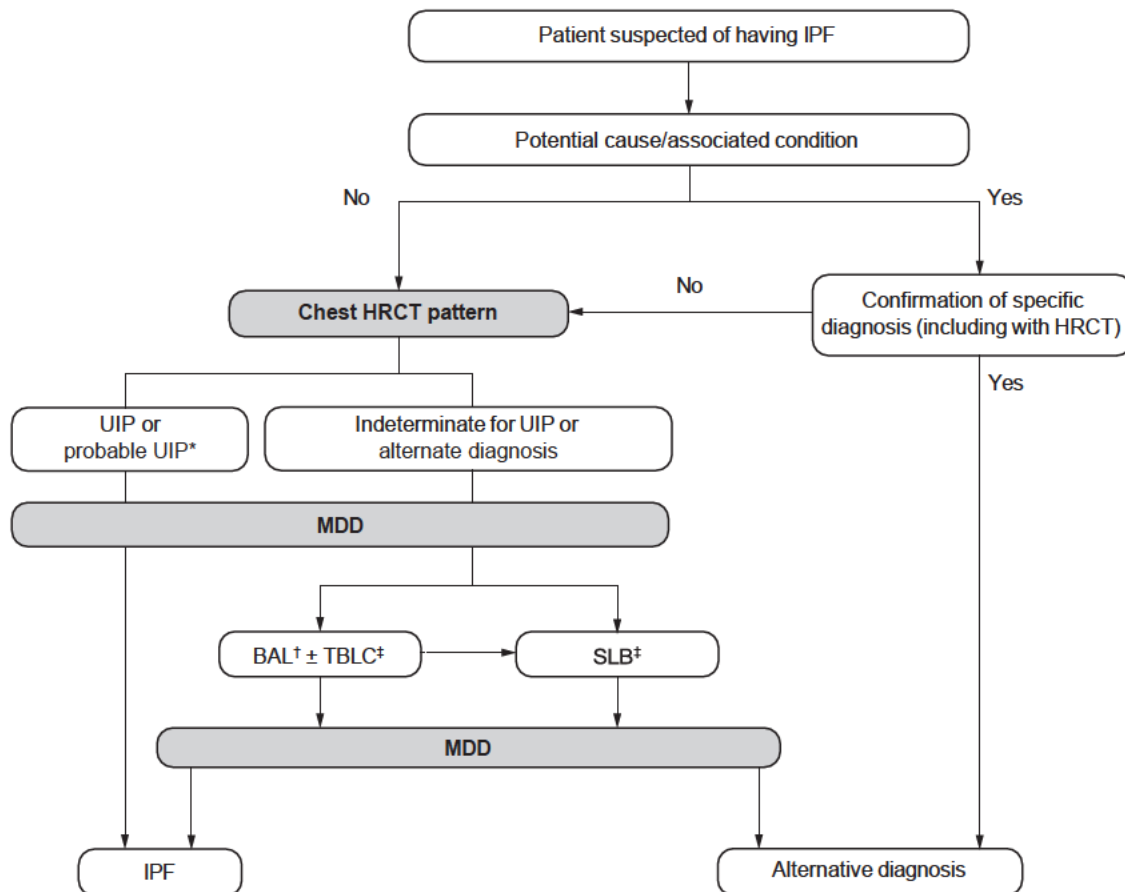


Figure 10. Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF), developed using consensus by discussion. *Patients with a radiological pattern of probable usual interstitial pneumonia (UIP) can receive a diagnosis of IPF after multidisciplinary discussion (MDD) without confirmation by lung biopsy in the appropriate clinical setting (e.g., 60 yr old, male, smoker). BAL may be appropriate in some patients with a probable UIP pattern. †BAL may be performed before MDD in some patients evaluated in experienced centers. ‡Transbronchial lung cryobiopsy (TBLC) may be preferred to surgical lung biopsy (SLB) in centers with appropriate expertise and/or in some patient populations, as described in the text. A subsequent SLB may be justified in some patients with nondiagnostic findings on TBLC. Adapted from Reference 2. HRCT = high-resolution computed tomography.

Studies included a small, randomized trial that compared the effects of omeprazole and placebo (86), 12 observational studies (4 of which enrolled patients from antifibrotic randomized trials) that compared proton pump inhibitors and/or histamine-2 receptor antagonists with no antacid medication at baseline (83, 84, 87–96), and 2 case series that evaluated proton pump inhibitors and/or histamine-2 receptor antagonists without a control group (80, 97). Ten studies evaluated proton pump inhibitors and/or histamine-2 receptor antagonists (83, 84, 87, 89–92, 94, 96, 97), and the remaining 5 studies evaluated proton pump inhibitors only (80, 86, 88, 93, 95).

DISEASE PROGRESSION. When the data from two observational studies were aggregated by meta-analysis, antacid medication had no statistically significant

effect on disease progression when defined as a composite of .10% decline in FVC, .50-m decline in 6-minute-walk distance (6MWD), or death (91, 92). An observational study of 1,061 patients that was not included in the meta-analysis because it defined disease progression differently showed that antacid medication was not associated with a statistically significant effect on disease progression when defined as a composite of >5% decline in FVC or death; however, it was associated with increased disease progression when defined as a composite of >10% decline in FVC or death (87).

MORTALITY. A small randomized trial found no significant difference in 90-day mortality when a proton pump inhibitor was compared with placebo (86), and multiple observational studies that reported mortality

at time points ranging from 30 weeks to 5 years all revealed no significant difference when antacid medication was compared with no medication (84, 91, 92, 96). Only the 1-year time point was reported by multiple observational studies and therefore could be evaluated by a meta-analysis, which showed no significant difference when antacid medication was compared with no antacid medication (91, 92, 96). There were similarly no differences in IPF-related mortality according to four observational studies (91–93, 95).

EXACERBATIONS AND HOSPITALIZATIONS. Meta-analyses of observational studies detected no statistically significant effect on exacerbations over a 30-week to 1-year follow-up period (84, 87) or hospitalizations over a 90-day to 1-year follow-up period (84, 91, 92). A small

randomized trial similarly showed no effect on hospitalizations at 90 days (86).

LUNG FUNCTION. A meta-analysis of three observational studies showed no difference in the change of percentage predicted FVC when patients who received antacid medication were compared with those who did not receive antacid medication (89, 91, 92). Additional observational studies similarly demonstrated no differences in the change in FVC or 6MWD between patients with and without antacid medication over 30 weeks to 1 year (84, 91, 92). A small randomized trial showed that FVC and percentage predicted FVC were both decreased at 90 days in the omeprazole group, but not the placebo group, with no differences in DL_{CO} or 6MWD (86).

ADVERSE EFFECTS. One small randomized trial (86) and three observational studies (87, 91, 92) evaluated adverse effects of antacid medication in patients with IPF. In the randomized trial, there was no difference in any adverse effect, severe adverse effects, or specific adverse effects at 90 days (86). Two observational studies looked at specific types of adverse effects and revealed no difference in the antacid medication group compared with the control group at 1 year (91, 92). In the third observational study, there was no difference in the rate of any adverse effect, but there was a higher rate of serious adverse effects in the antacid medication group compared with the control group, although the study had limitations that were acknowledged by its authors (87).

QUALITY OF EVIDENCE. The quality of evidence for all outcomes was rated as very low, meaning that the committee should have very low confidence in the estimated effects, and therefore, the effects summarized below should be interpreted with caution. The main reason for the very low quality rating was that the critical outcomes were informed primarily by observational studies, many of which had a risk of immortal time bias. The lone randomized trial was limited by imprecision and short follow-up.

Guideline committee conclusions. The pertinent evidence was observational and indirect (i.e., the question was about patients with IPF who had confirmed GER, but the evidence consisted of unselected patients with IPF, both with and without confirmed GER). The committee discussed whether guidance should be provided for patients with IPF plus confirmed GER (i.e., the original question) or for all patients with IPF

regardless of whether GER was confirmed or not (i.e., the population for which direct evidence exists), then voted by a two-thirds majority to provide guidance for all patients with IPF regardless of whether GER was confirmed. In the absence of any definitive benefits, the committee voted to make a conditional recommendation against treating patients with IPF with antacid medication for the sole purpose of improving respiratory outcomes.

The committee emphasized three things, however. First, it is possible that antacid therapy may have beneficial effects in patients with confirmed GER that were negated by the inclusion of patients with IPF without GER in studies that enrolled all patients with IPF; therefore, the guidance might change if patients with IPF are stratified as either having or not having confirmed GER and the efficacy of antacid medication is determined for each subgroup. Second, the quality of evidence was very low, meaning that the committee had very low confidence in the estimated effects, which should be interpreted with caution. Finally, antacid medication may be indicated in patients with IPF with symptoms of GERD to improve GER-related outcomes, and the committee refers readers to GER-specific clinical practice guidelines.

Guideline committee vote. The committee's vote was as follows: strong recommendation for antacid medication, 0 of 28 (0%); conditional recommendation for antacid medication, 2 of 28 (7%); conditional recommendation against antacid medication, 24 of 28 (86%); and strong recommendation against antacid medication, 2 of 28 (7%). Three participants abstained from voting, 1 citing insufficient evidence and 2 indicating that they believed they had insufficient expertise.

Research needs. The predominance of existing evidence is observational and, therefore, susceptible to bias due to unmeasured confounders. Randomized trials comparing the effects of antacid medication and placebo on respiratory outcomes in patients with IPF would be a valuable addition to the field, potentially enabling definitive recommendations. Theoretically, antacid therapy may have a differential effect in patients with confirmed or symptomatic GER, so randomized trials should be powered to look at these subgroups.

We suggest not referring patients with IPF for antireflux surgery for the purpose of improving respiratory outcomes

(conditional recommendation, very low quality evidence). Remarks: Antireflux surgery may be appropriate for patients with both IPF and symptoms of GERD for the purpose of improving GER-related outcomes in accordance with GER-specific guidelines.

Background. Antireflux surgery to improve respiratory outcomes in patients with IPF has never been considered in the context of a clinical practice guideline.

Summary of evidence. The committee asked, "Should patients with IPF and confirmed GER, with or without symptoms of GERD, be referred for antireflux surgery to improve respiratory outcomes?" The systematic review that informed the committee's recommendation is published independently (85); we summarize the salient findings. Five outcomes were designated as critical: disease progression, mortality, exacerbations, hospitalizations, and lung function. Two outcomes were designated as important: GER severity and adverse effects.

The systematic review identified four studies that evaluated antireflux surgery in patients with IPF. The number of participants ranged from 27 to 204. Studies included a small randomized trial comparing antireflux surgery with no surgery (98), 2 observational studies comparing antireflux surgery with no surgery (83, 99), and 1 case series of patients who underwent antireflux surgery without a control group (100). The randomized trial required that patients have confirmed GER, whereas the observational studies and case series indicated that most patients had GER confirmed before surgery. Surgical procedures included any type of fundoplication, which was performed laparoscopically in three studies.

DISEASE PROGRESSION. The randomized trial of 58 patients with IPF measured the effect of antireflux surgery on disease progression using various composite outcomes over 48 weeks: 1) .10% decline in FVC or death; 2) .10% decline in FVC, acute exacerbation, or death; 3) respiratory hospitalization or death; 4) nonelective hospitalization or death; or 5) 10% decline in FVC, 5-point change in University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ), respiratory hospitalization, or death (98). The first and second outcomes showed no effects when analyzed using relative risk and 95% confidence intervals but reached statistical significance when an adjusted *P* value was derived using a worst-rank analysis. The

third, fourth, and fifth outcomes showed no effects with either a relative risk and 95% confidence interval analysis or a worst-rank analysis. An observational study of 34 patients used change in oxygen requirement as a surrogate for disease progression and demonstrated decreasing oxygen requirements in the surgery group and increasing oxygen requirements in the no-surgery group over a mean follow-up period of 15 months (99).

MORTALITY. The randomized trial showed no statistically significant effect on overall mortality at 48 weeks (98), while an observational study of 204 patients with IPF reported no significant association between antireflux surgery and overall mortality after a median follow-up period of .3 years (83).

EXACERBATION AND HOSPITALIZATION. Only the randomized trial measured exacerbation and hospitalization rates. The trial reported no statistically significant effect on exacerbations, respiratory-related hospitalizations, or all hospitalizations (98).

LUNG FUNCTION. There were no differences in either absolute measurements and/or changes in FVC, DLCO, or 6MWD in either the randomized trial (98) or an observational study of 34 patients (99).

SURGICAL COMPLICATIONS. Surgical complications were reported in the randomized trial (98), one of the observational studies (99), and the case series (100). The aggregate 30-day rates of all surgical complications and severe surgical complications were 15% and 9%, respectively (98–100). Among the more common complications, dysphagia, abdominal distension, and nausea occurred in 18%, 15%, and 4% of patients, respectively.

QUALITY OF EVIDENCE. The quality of evidence for all outcomes was rated as very low, meaning that the committee should have very low confidence in the estimated effects, and therefore, the effects summarized below should be interpreted with caution. The main reason for the very low quality rating was that many of the critical outcomes were informed by a randomized trial that was downgraded because of risk of bias (lack of blinding, crossover), imprecision (wide confidence intervals because of few events), and potential reporting bias (some secondary outcomes were not reported). Other outcomes were informed by observational evidence limited by small size and incomplete data availability for some outcomes.

Guideline committee conclusions. In the absence of any definite statistically significant benefits but surgical complications occurring in up to 15% of patients, the committee voted to make a conditional recommendation to not refer patients for antireflux surgery for the purpose of improving respiratory outcomes. However, the committee emphasized three things. First, many of the point estimates would be clinically important if real, but the confidence intervals extend from a large beneficial effect to harm, indicating that the sample size was too small to definitively confirm or exclude an effect. This suggests a need for further research to investigate these outcomes. Second, the quality of evidence is very low, meaning that the committee should have very low confidence in estimated effects. Finally, the conditional recommendation is about whether patients should be referred for antireflux surgery for the sole purpose of improving respiratory outcomes and is not intended as a judgment about the value of antireflux surgery to improve GER-related outcomes in patients with IPF. The latter may be appropriate in some situations.

Guideline committee vote. The committee's vote was as follows: strong recommendation for referral for antireflux surgery, 0 of 28 (0%); conditional recommendation for referral for antireflux surgery, 7 of 28 (25%); conditional recommendation against referral for antireflux surgery, 15 of 28 (54%); and strong recommendation against referral for antireflux surgery, 6 of 28 (21%). Two participants abstained from voting, both indicating that they had inadequate expertise to address the question.

Research needs. The prevailing observation from the systematic review was that a single randomized trial exists that measured clinically meaningful outcomes and whose point estimates suggest a potential beneficial effect, but the trial was too small to either confirm or exclude such an effect. Thus, a larger, adequately powered randomized trial comparing antireflux surgery with no surgery in patients with confirmed GER is needed, with measurement of the same or similar outcomes as the existing randomized trial (98).

Management

The committee updated a key figure summarizing the management of IPF from the 2011 IPF guidelines (Figure 11) (1).

Approach

Future

Research needs related to TBLC, genomic classifier testing, antacid medications, and antireflux surgery are addressed above. Additional needs include the following:

- Validate the utility of family history or genetics in diagnostic algorithms, as incorporating family aggregation and genetic data into the MDD might avoid invasive procedures (31, 101–106).
- Evaluate combination therapies (107–112).
- Optimize strategies for addressing quality of life, including treatment of comorbidities, physical activity, emotional well-being, and palliation of symptoms (31, 113–123).

Directions

Part II: Diagnosis and Treatment of PPF in Fibrotic ILD, Other than IPF

Definition of PPF

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation (Table 4):

1. worsening respiratory symptoms;
2. physiological evidence of disease progression, as defined below; and
3. radiological evidence of disease progression, as defined below.

Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in DLCO given the lower specificity of these features for PPF compared with FVC and chest CT.

The guideline committee emphasized four points. First, PPF is defined separately from IPF, which was defined in previous guidelines (1, 2) (Figure 12). Second, PPF is not a diagnosis, and the definition of PPF is agnostic to the underlying condition. Representative fibrotic lung diseases that can manifest PPF are listed in Table 5. Third, the criteria for PPF reflect multiple clinical trials because the committee believed that no single trial should guide antifibrotic therapy.

Even though trials used different criteria, they identified populations whose disease progressed similarly. Finally, the criteria for PPF have been associated only with prognosis; it is unclear if they also identify patients best suited for antifibrotic therapy.

The guideline committee considered other terms. They contemplated whether to maintain the term used in a hallmark clinical trial (4), “progressive fibrosing ILD,” but opted to adopt the term “PPF” instead because 1) disease progression is the result of PPF beyond the interstitial space in the lung parenchyma; 2) disease progression causes a clinical course similar to IPF; and 3) PPF is simple and compatible with the broadly used term that is well known and currently used by both clinicians and patients, “pulmonary fibrosis.” The committee also considered incorporating the term “phenotype” (e.g., progressive fibrotic phenotype). However, “phenotype” implies that there is an identified genotype, but there is no known genotype associated with PPF. The committee was not in favor of using “clinical phenotype,” because this was unlikely to be distinguished from “phenotype” by most clinicians.

Physiological Criteria for PPF

There is a paucity of published data regarding physiological measurements in patients with PPF. Therefore, the committee derived the physiological criteria for PPF by extrapolation of data from patients with IPF because the disease behavior and prognosis of IPF and PPF are comparable (124). The committee defined physiological evidence of disease progression as the presence of either of the following findings, if the findings are attributable to worsening fibrosis:

1. Absolute decline in FVC of $>5\%$ within 1 year of follow-up.
2. Absolute decline in DL_{CO} (corrected for Hb) of $>10\%$ within 1 year of follow-up.

Several physiological criteria were discussed, including changes in FVC, DL_{CO} , and walk distance; acute exacerbations; hospitalizations; deteriorated or newly developed pulmonary hypertension; and change in quality of life. Only changes in FVC and DL_{CO} were accepted by the guideline committee, as all other factors are highly variable or may be altered by the clinical context (e.g., hospitalization patterns).

Absolute decline in FVC. FVC is the physiological parameter most often used to follow patients with IPF because it is associated with prognosis (125). The guideline committee chose an absolute decline in FVC of $>5\%$ over 1 year as a criterion for disease progression, a value that was extrapolated from the IPF literature.

Although some trials have used a relative change in FVC to assess progression of pulmonary fibrosis, the committee prefers to use absolute change because it forecasts poorer outcomes and is regarded as an important predictor of mortality in IPF (126). It is important to understand that absolute and relative changes in FVC identify different populations. For example, a patient beginning with an FVC of 60% predicted would be determined to have progressive disease at an FVC of 55% if defined as an absolute decline of $>5\%$ but would be determined to have progressive disease at an FVC of 57% if defined as a relative decline of $>5\%$. The absolute decline in FVC is calculated as the initial FVC measurement minus the final FVC measurement (example 1: 60% predicted minus 55% predicted equals a 5% absolute decline; example 2: 1,000 ml minus 950 ml equals a 50-ml absolute decline), whereas a relative decline in FVC is calculated as the difference between the initial and final FVC measurements, divided by the initial FVC measurement (example 1: [60% predicted minus 57% predicted] divided by 60% predicted equals a 5% relative decline; example 2: [1,000 ml minus 950 ml] divided by 1,000 ml equals a 5% absolute decline).

Highlighting the importance of FVC as a measure of disease progression, FVC has been used to define disease progression in recent trials on patients with PPF, including the INBUILD (Efficacy and Safety of Nintedanib in Patients with Progressive Fibrosing Interstitial Lung Disease) trial (4), the RELIEF (Exploring Efficacy and Safety of Oral Pirfenidone for Progressive, Non-IPF Lung Fibrosis) trial (127), and a trial of patients with unclassifiable ILD (uILD) (128). According to one retrospective analysis, there can be significant differences in the course of disease depending on the criteria used to define progression (129).

Absolute decline in DL_{CO} . DL_{CO} has not been a successful endpoint in clinical trials of patients with pulmonary fibrosis, likely because of measurement variability within patients, varying techniques across pulmonary function laboratories, and lack of

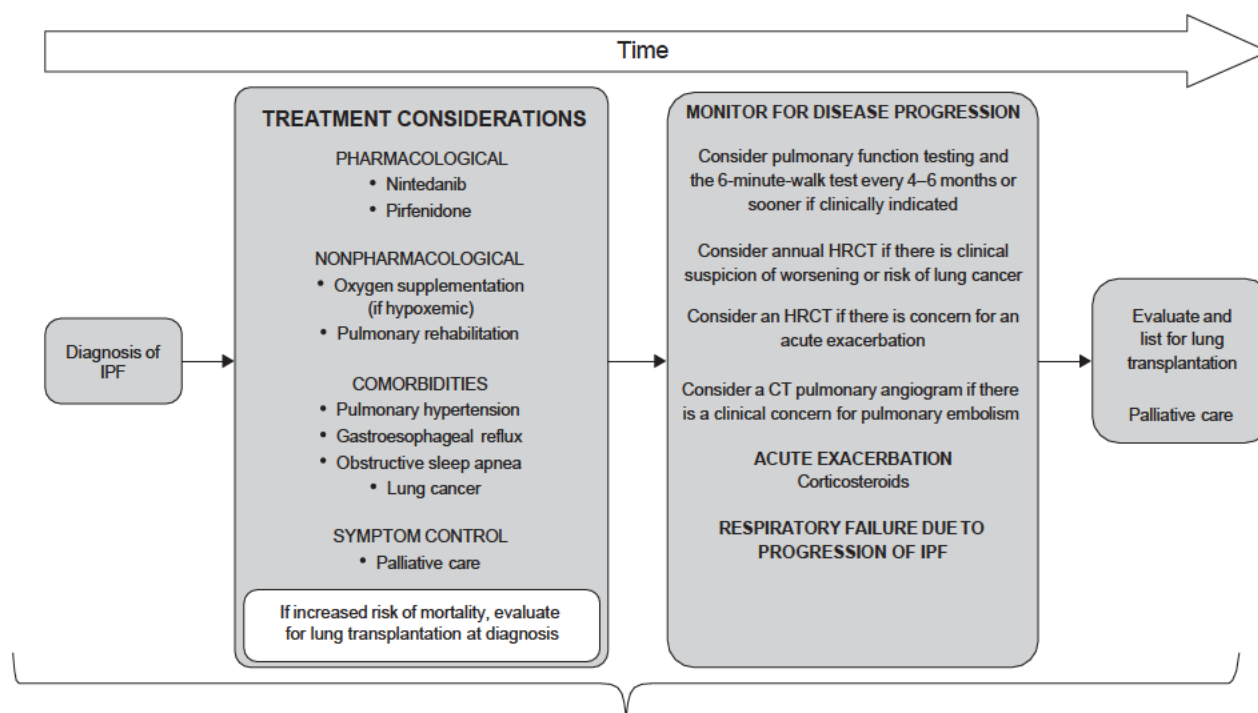
specificity for progression of pulmonary fibrosis. Despite these limitations, change in DL_{CO} (corrected for Hb) is a consistent and strong predictor of mortality in patients with a variety of fibrotic lung diseases (130, 131). The committee’s inclusion of DL_{CO} as a criterion for PPF is justified on this basis, with the caveat that it is essential to exclude alternative causes of worsening DL_{CO} before ascribing any decline in DL_{CO} to progressive fibrosis. The requirement that a decline in DL_{CO} be attributed to progressive fibrosis mandates the performance of additional evaluation, typically including HRCT, to exclude alternative causes of worsening DL_{CO} . Hb-corrected decline in absolute measurements of DL_{CO} in the absence of another explanation for the decline may be a sign of PPF, especially when complemented by a decrease in FVC or increased extent of fibrosis on HRCT.

The committee defined a clinically meaningful decline in DL_{CO} as an absolute decline of $>10\%$, justifying the higher threshold on the basis of technical limitations affecting the reproducibility of this measurement. As with FVC, the committee prefers to use absolute change rather than relative change for DL_{CO} . For example, a patient beginning with a DL_{CO} of 60% predicted would be determined to have progressive disease at a DL_{CO} of 50% or lower if defined as an absolute decline of $>10\%$ but would be determined to have progressive disease at a DL_{CO} of 54% or lower if defined as a relative decline of $>10\%$.

An additional criterion that was considered by the committee was acute exacerbation, but this was deemed not appropriate for the definition of PPF because it has its own separate definition (132). In practice, clinicians should reassess patients after exacerbations and use these assessments to determine if progression occurred.

Radiological Criteria for PPF

Visual determination of progression of pulmonary fibrosis. Progression of fibrosis is typically assessed visually, relying on the percentage of lung volume containing fibrotic features in the upper, mid, and lower lung zones. Transverse, coronal, and sagittal contiguous HRCT sections of the initial and follow-up CT examinations are compared side by side, after adjustment for lung volume changes. An increased extent of fibrotic features denotes progression



Patients should be made aware of available clinical trials for possible enrollment at all stages

Figure 11. Schematic pathway for clinical management of patients with idiopathic pulmonary fibrosis (IPF), developed using consensus by discussion. Treatment considerations should include both pharmacological (nintedanib and pirfenidone) and nonpharmacological (oxygen supplementation and/or pulmonary rehabilitation) therapies. Patients should be evaluated and treated for existing comorbidities, including pulmonary hypertension, gastroesophageal reflux, obstructive sleep apnea, and lung cancer. Patients may benefit from involvement of palliative care to help with symptom management (cough, dyspnea, and/or anxiety). Patient values and preferences should be explored. Patients at increased risk of mortality should be referred for lung transplantation at diagnosis. Patients should be evaluated every 3–6 months or more often for disease progression. Acute exacerbations may be treated with corticosteroids. Mechanical ventilation is not recommended for the majority of patients with respiratory failure. Adapted from Reference 1. CT = computed tomography; HRCT = high-resolution computed tomography.

Table 4. Definition of Progressive Pulmonary Fibrosis

Definition of PPF
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:
1 Worsening respiratory symptoms
2 Physiological evidence of disease progression (either of the following):
a. Absolute decline in FVC >5% predicted within 1 yr of follow-up
b. Absolute decline in DL _{CO} (corrected for Hb) >10% predicted within 1 yr of follow-up
3 Radiological evidence of disease progression (one or more of the following):
a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
b. New ground-glass opacity with traction bronchiectasis
c. New fine reticulation
d. Increased extent or increased coarseness of reticular abnormality
e. New or increased honeycombing
f. Increased lobar volume loss

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.

*Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in DL_{CO} given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

(Figure 13). These may include increased traction bronchiectasis and bronchiolectasis, new ground-glass opacity with traction bronchiectasis, new fine reticulation, increased coarseness of reticular abnormality, new or increased honeycombing, and increased lobar volume loss.

In IPF, progression is usually manifested by increased extent of the UIP pattern, in both transverse and coronal planes (133–135). The size and number of honeycomb cysts often increase as the disease progresses. Progression of traction bronchiectasis and bronchiolectasis is a strong independent predictor of mortality in IPF (136). In ILDs other than IPF, however, the pattern of progression is variable and may include evolution of ground-glass abnormality to reticular abnormality (134, 137), evolution of reticular abnormality to honeycombing (137), and/or increase in traction bronchiectasis/bronchiolectasis.

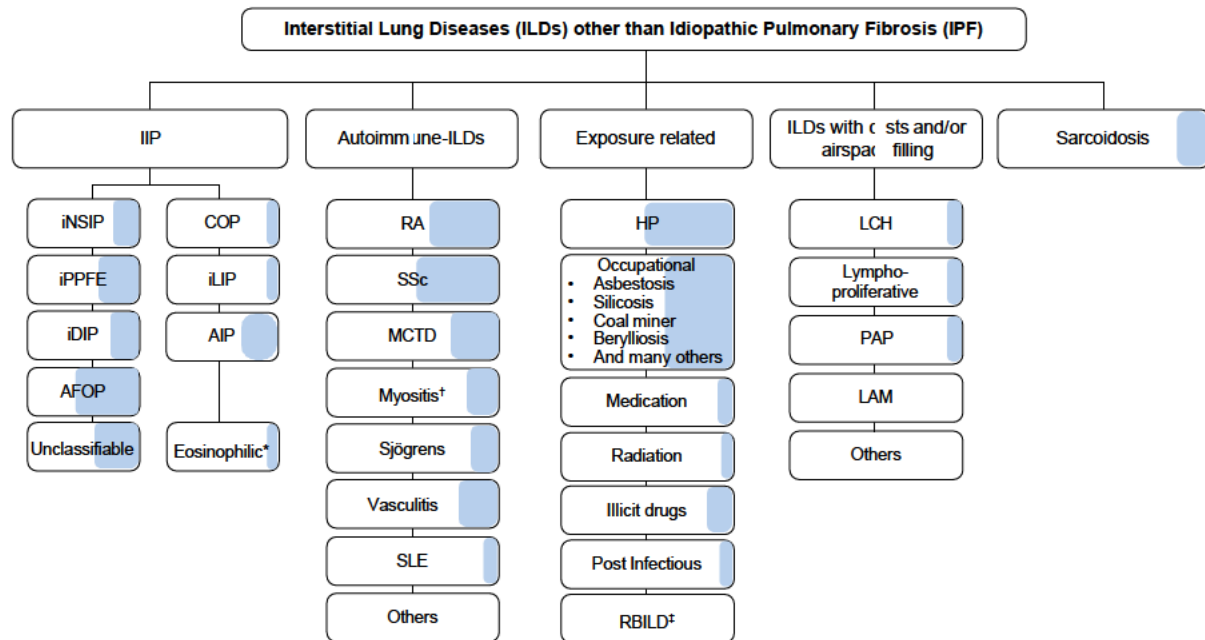


Figure 12. Interstitial lung diseases (ILDs) manifesting progressive pulmonary fibrosis (PPF), developed using consensus by discussion. The shaded area represents the estimated proportion of patients with various types of ILD who manifest PPF. Note that idiopathic pulmonary fibrosis (IPF) is not included in the figure, because it is excluded from the definition of PPF. While virtually all patients with IPF will manifest disease progression similar to PPF, the proportion of patients with ILDs other than IPF who manifest PPF is based on the consensus of opinions and the perception of the international committee. There are no data to provide the exact or estimated proportion of patients manifesting PPF in ILDs, other than IPF. *The committee acknowledges that eosinophilic pneumonia of unknown cause was not included in the IIP classification. †Myositis includes PM/DM/antisynthetase syndrome, which may be amyopathic. ‡Although respiratory bronchiolitis interstitial lung disease (RBILD) is acknowledged to be a consequence of exposure to cigarette smoke in virtually all patients with RBILD, RBILD and desquamative interstitial pneumonia (DIP) often coexist. Although DIP is also related to exposure to cigarette smoke in a majority of patients, DIP is also seen in some patients with connective tissue disease, without exposure to cigarette smoke, and without a known cause. Antifibrotic treatment is indicated for patients diagnosed with IPF (3). Antifibrotic treatment of the other types of ILD upon manifesting PPF is as suggested/recommended in this guideline. AFOP = acute fibrinous and organizing pneumonia; AIP = acute interstitial pneumonia; COP = cryptogenic organizing pneumonia; DM = dermatomyositis; HP = hypersensitivity pneumonitis; iDIP = idiopathic DIP; IIP = idiopathic interstitial pneumonia; iLIP = idiopathic lymphoid interstitial pneumonia; iNSIP = idiopathic nonspecific interstitial pneumonia; iPPFE = idiopathic pleuroparenchymal fibroelastosis; LAM = lymphangioleiomyomatosis; LCH = Langerhans cell histiocytosis; MCTD = mixed connective tissue disease; PAP = pulmonary alveolar proteinosis; PM = polymyositis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

Patients with nonspecific interstitial pneumonia (NSIP) may progress to a UIP-like CT pattern with honeycombing (137–139) (Figure 14).

Follow-up HRCT is indicated when there is clinical suspicion of worsening fibrosis. The optimal interval for follow-up HRCT to determine disease progression is unknown. Limited data suggest that in patients with systemic sclerosis and stable pulmonary function, repeated chest HRCT within 12–24 months from baseline could be useful to promptly detect progression and possibly influence prognosis (140). Annual HRCT can also be considered to screen for complications, particularly lung cancer.

It is difficult to predict the proportion of patients with non-IPF ILDs who will develop a progressive fibrotic pattern; however, some HRCT findings in individual patients are considered predictors of disease progression. For example, in addition to the presence of honeycombing and traction bronchiectasis, which are associated with worse prognosis, a greater extent of fibrotic changes is known to be predictive of mortality in IPF, rheumatoid arthritis-related ILD, systemic sclerosis-related ILD, fibrotic HP, pulmonary sarcoidosis, and uILD (141).

CT features of early lung fibrosis include fine reticulation, intralobular lines,

and architectural distortion (irregular, tortuous pulmonary vessels and airways or distorted lobular anatomy), seen either in isolation or superimposed on ground-glass opacities. This pattern, suggestive of interstitial changes at an early phase, may be seen incidentally on thoracic or abdominal CT scans obtained for other purposes, including screening for lung cancer, and is often associated with histologic evidence of fibrosis (142). These incidentally identified interstitial lung abnormalities (ILA) (143) are an independent risk factor for mortality. At least 40% of subjects with ILA show progression of CT changes when followed over 4–6 years (142) (see Figure E1 in the online supplement).

Table 5. Selected Fibrotic Lung Diseases That Can Manifest Progressive Pulmonary Fibrosis

Potentially Fibrotic Interstitial Lung Diseases	Histologic Patterns
Idiopathic F-NSIP	• F-iNSIP (179)
PPFE	• IAFE (179) • May coexist with other patterns such as UIP in patients with other forms of concomitant ILD (e.g., IPF) (180)
FOP	• Cicatricial organizing pneumonia (181) • Organizing pneumonia with concomitant interstitial fibrosis (sometimes secondary to diffuse alveolar damage/acute interstitial pneumonia) (179, 182)
DIP	• DIP*
Fibrotic CTD-related ILD	• F-NSIP, FOP, UIP (use histopathological criteria for idiopathic diseases [179])
Fibrotic HP	• HP and probable HP (138) • Fibrotic element may be that of UIP, F-NSIP, or bronchiolocentric fibrosis
Fibrotic occupational ILD	• Dependent on occupational lung disease (asbestosis, fibrotic HP, silicosis, pneumoconiosis, or other) (183)
Fibrotic LCH	• F-LCH (184)
Fibrotic sarcoidosis	• Discrete nonnecrotizing granulomas with a lymphatic distribution with coexistent fibrosis (185)
Unclassified fibrotic ILD	• Cases should ideally be termed “unclassifiable” only after multidisciplinary discussion. Most cases represent combined or overlapping patterns of classifiable interstitial pneumonias, and these should be reported as such (179)
Other	• Fibrosis in association with inborn errors of metabolism, surfactant protein disorders, pulmonary involvement by systemic disorders, or others

Definition of abbreviations: CTD = connective tissue disease; DIP = desquamative interstitial pneumonia; F-LCH = fibrotic Langerhans cell histiocytosis; F-iNSIP = fibrotic idiopathic nonspecific interstitial pneumonia; F-NSIP = fibrotic nonspecific interstitial pneumonia; FOP = fibrosing organizing pneumonia; HP = hypersensitivity pneumonitis; IAFE = intraalveolar fibrosis and elastosis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LCH = Langerhans cell histiocytosis; PPFE = pleuroparenchymal fibroelastosis; UIP = usual interstitial pneumonia.

*Terminology for fibrotic interstitial pneumonias with DIP-like features is controversial, this overlapping with F-NSIP.

Quantitative assessment of progression of pulmonary fibrosis. Computer-based quantitative CT (QCT) can provide a more objective and reproducible measure of progression than visual assessment (144, 145) (Figure E2). QCT has evolved from relatively simple histogram-based techniques (146, 147) to machine learning methods based on texture (112, 148–152), local histogram (31, 153–158), and deep learning–based classification (159–161). These approaches have successfully defined the extent and progression of disease and predicted mortality. Further validation and adoption of standardized protocols will be necessary before QCT can be widely used in the community.

Evidence-based Recommendations for Treatment of PPF, Other than IPF

Pirfenidone. We recommend further research into the efficacy, effectiveness, and safety of pirfenidone in both 1) non-IPF ILD

manifesting PPF in general and 2) specific types of non-IPF ILD manifesting PPF.

BACKGROUND. It is plausible that antifibrotic agents that slow disease progression in IPF may also slow progression in PPF. One such antifibrotic agent, pirfenidone, is an oral agent with antiinflammatory, antioxidative, and antiproliferative effects that was recommended for treatment of IPF in prior guidelines (3).

The committee asked, “Should patients with PPF be treated with pirfenidone?” Given that many different types of ILD can manifest PPF, this overarching question was also asked for eight specific types of ILD that can manifest PPF: 1) Should patients with PPF and radiological UIP pattern be treated with pirfenidone? 2) Should patients with PPF and radiological non-UIP pattern be treated with pirfenidone? 3) Should patients with progressive fibrotic HP be treated with pirfenidone? 4) Should patients with progressive fibrotic CTD-related ILD be treated with pirfenidone? 5) Should patients

with progressive fibrotic NSIP be treated with pirfenidone? 6) Should patients with progressive fibrotic sarcoidosis be treated with pirfenidone? 7) Should patients with progressive fibrotic occupational ILD be treated with pirfenidone? 8) Should patients with progressive fibrotic uILDs be treated with pirfenidone?

Critical outcomes included mortality and disease progression (determined by change in FVC). Important outcomes included lung function (determined by changes in FEV₁, TLC, DLCO, and 6MWD), respiratory symptoms (determined by change in St. George’s Respiratory Questionnaire, Leicester Cough Questionnaire, UCSD-SOBQ, or visual analog scale for cough scores), and adverse events (AEs).

SUMMARY OF EVIDENCE. The systematic review that informed the committee’s recommendation is published independently (162); we summarize the salient findings. The systematic review identified two randomized trials that enrolled

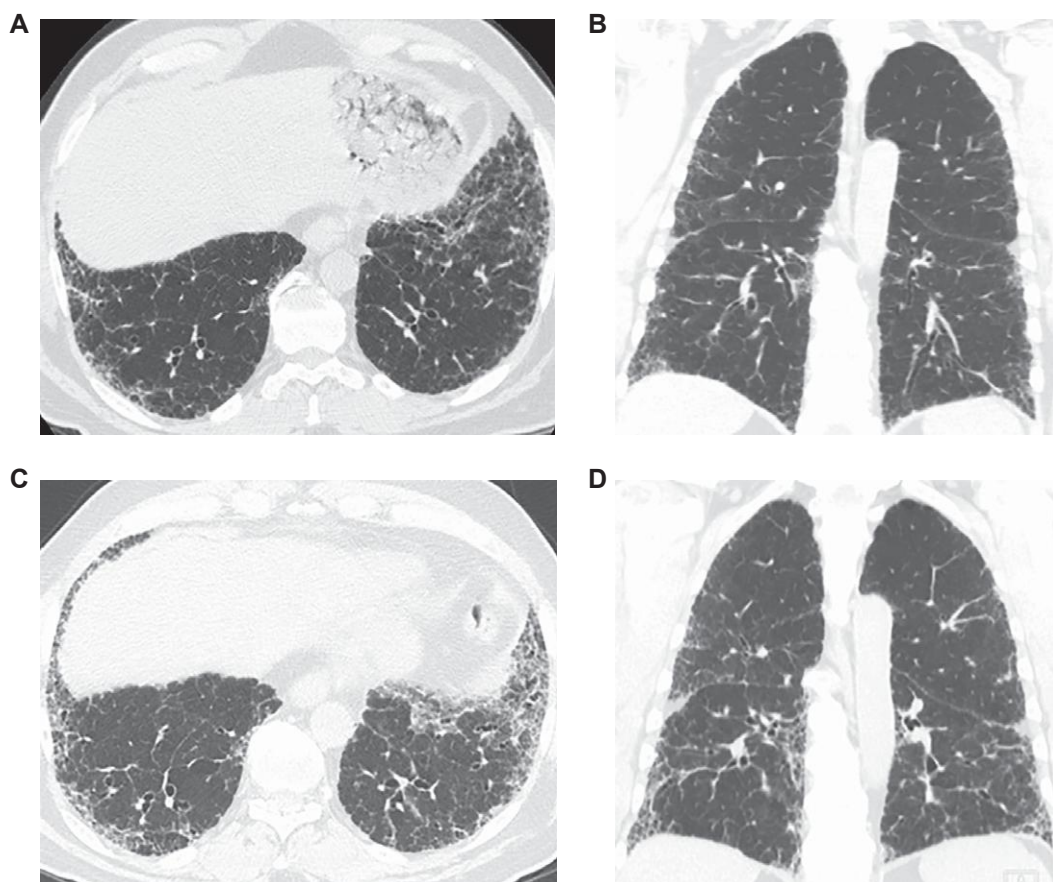


Figure 13. Progressive pulmonary fibrosis in a patient with idiopathic pulmonary fibrosis (probable usual interstitial pneumonia pattern). (A and B) Baseline axial and coronal images show moderately extensive reticular abnormality with traction bronchiectasis, with predominance in the subpleural lower lung. (C and D) Matched images 4 years later show substantial increase in extent of abnormality and increased traction bronchiectasis.

patients with PPF and evaluated the effects of pirfenidone (127, 128). One trial of uILD randomly assigned 253 patients with fibrotic uILD to receive pirfenidone or placebo, then followed them for 24 weeks (128). The other trial (RELIEF) randomly assigned 127 patients with PPF to receive pirfenidone or placebo, then followed them for 48 weeks (127). The latter trial included patients with chronic HP, CTD-related IILD, NSIP, and asbestosis-induced lung fibrosis. The trial was terminated early because of futility triggered by slow recruitment; however, imputations were conducted for missing data with the primary analysis favoring the pirfenidone arm.

Disease progression. When the trials were aggregated by meta-analysis, pirfenidone reduced the decreases in FVC by 100 ml and in percentage predicted FVC by 2.3% over 24 weeks (127, 128). In the uILD trial, pirfenidone decreased by 1.6 times the likelihood that percentage predicted FVC would decline .5% and decreased by 1.9

times the likelihood that percentage predicted FVC would decline .10% (128).

Mortality. The uILD trial did not demonstrate a statistically significant difference in progression-free survival (128). Similarly, the RELIEF trial did not show a statistically significant difference in progression-free survival or mortality at 48 weeks (127).

Lung function. Only the RELIEF trial reported changes in FEV₁ and TLC, neither of which was statistically significant (127). The RELIEF trial showed that pirfenidone reduced the mean decrease in DL_{CO} by 0.40 mmol/kPa/min (127), while the uILD trial found that patients with fibrotic uILD who received pirfenidone had a 3.7-times reduced risk of a DL_{CO} decline of .15%, although there was no statistically significant difference in the mean change in percentage predicted DL_{CO} (128). When the trials were combined by meta-analysis, pirfenidone attenuated the decline in 6MWD by 25.2 m, whereas in the uILD trial the

number of patients whose 6MWD declined by .50 m was unchanged (127, 128).

Respiratory symptoms. There was no significant difference in mean St. George's Respiratory Questionnaire score, Leicester Cough Questionnaire score, UCSD-SOBQ scores, or visual analog scale score for cough (127, 128).

AEs. Pirfenidone increased the risk of gastrointestinal discomfort 1.8 times and photosensitivity 4.9 times. Pirfenidone increased the risk of any AE 1.2 times and the risk of treatment-related AEs 1.5 times (128).

Quality of evidence. The quality of evidence for all outcomes was rated as very low, meaning that the committee should have very low confidence in the estimated effects, and therefore, the effects summarized below should be interpreted with caution. The main reason for the very low quality rating was that although there were two randomized trials, one trial was terminated early because of futility, and both trials were

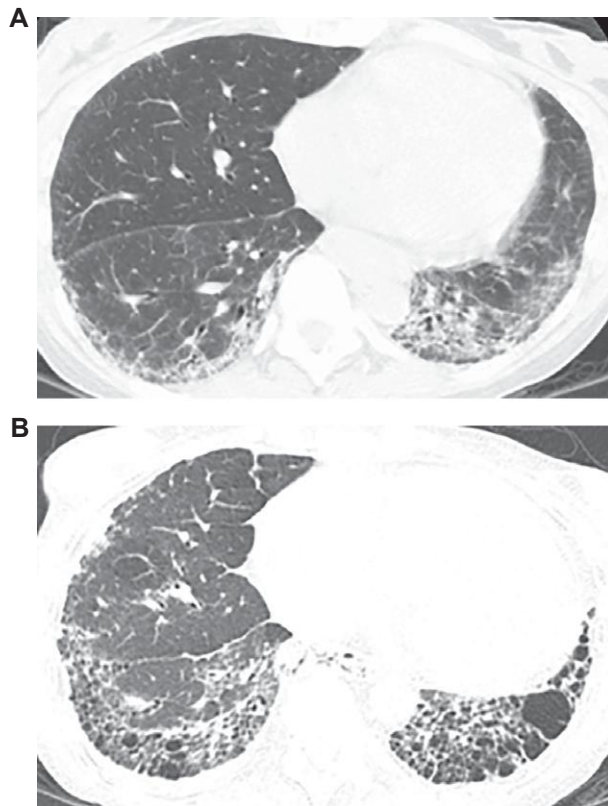


Figure 14. Progressive pulmonary fibrosis due to fibrotic nonspecific interstitial pneumonia (NSIP). (A) Computed tomography in a 45-year-old woman with scleroderma shows lower lung–predominant reticular and ground-glass abnormality with subpleural sparing, typical for NSIP. (B) Nine years later, the fibrosis has progressed with increased extent of reticular abnormality, increased traction bronchiectasis, and evolution of reticular abnormality to honeycombing. Small bilateral pleural effusions are present.

limited by small sample sizes, resulting in confidence intervals whose ends included both benefit and harm.

GUIDELINE COMMITTEE CONCLUSIONS.

Approximately one-third of the committee abstained from voting for or against pirfenidone, citing insufficient evidence, yielding a research recommendation according to prespecified voting rules. Among the committee members who were willing to vote for or against pirfenidone, there was unanimous consensus in favor of pirfenidone. The guideline committee as a whole acknowledged that pirfenidone is a promising therapy for non-IPF PPF but voiced two major concerns. First, they were concerned that the estimated effects informing their decisions derived from only 127 patients who had PPF due to an ILD other than fibrotic uILD, which was not precisely defined. Second, they were concerned that if they made a recommendation pertaining specifically to patients with uILD, it may discourage clinicians from rigorously trying to identify

the underlying type of ILD before the initiation of therapy, and the data are insufficient to warrant such a drastic paradigm shift.

GUIDELINE COMMITTEE VOTE. The committee's vote was as follows: strong recommendation for pirfenidone, 0 of 34 (0%); conditional recommendation for pirfenidone, 21 of 34 (62%); conditional recommendation against pirfenidone, 0 of 34 (0%); and strong recommendation against pirfenidone, 0 of 34 (0%). Thirteen participants (38%) abstained from voting, 11 citing insufficient evidence to make a recommendation and 2 citing insufficient expertise to render a thoughtful judgment.

RESEARCH NEEDS. The existing randomized trials encompass only 380 patients with PPF, among whom 253 had fibrotic uILD manifesting PPF. Additional randomized trials are needed that enroll patients with PPF due to other types of ILD, compare pirfenidone with placebo, and measure disease progression, mortality, and AEs. The number of patients should be

sufficient to allow independent analysis of each type of ILD.

Nintedanib.

- We suggest nintedanib for the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF (conditional recommendation, low-quality evidence). Remarks: Standard management will differ from patient to patient. In many patients it will be immunosuppressive treatment in an attempt to stabilize or reverse initial disease, but this is not a prerequisite, as in some patients, standard management could be antigen remediation or observation. Besides this, it should be acknowledged that in many ILDs, evidence-based guidance for standard of care is lacking; hence, standard of care may vary from region to region.
- We recommend research into the efficacy, effectiveness, and safety of nintedanib in specific types of non-IPF ILD manifesting PPF.

BACKGROUND. Nintedanib is another antifibrotic agent that, like pirfenidone, slows disease progression in IPF. It is an oral intracellular tyrosine kinase inhibitor that blocks pathways involved in fibrogenesis, which was recommended for treatment of IPF in prior guidelines (3).

The committee asked, "Should patients with PPF be treated with nintedanib?" Given that many different types of ILD can manifest PPF, this question was also asked for the same eight specific types of ILD that were described in the pirfenidone section above. Critical outcomes included mortality and disease progression (determined by change in FVC). Important outcomes included respiratory symptoms (determined by changes in the King's Brief Interstitial Lung Disease Questionnaire) and AEs.

SUMMARY OF EVIDENCE. The systematic review that informed the committee's recommendation is published independently (163); we summarize the salient findings. The systematic review identified one randomized trial (4) and a *post hoc* analysis of the trial (164). The randomized trial (INBUILD) randomly assigned 663 patients with PPF to nintedanib or placebo for 52 weeks, while the *post hoc* analysis compared the effects of nintedanib with placebo in the individual

types of ILD that were manifesting PPF. The type of ILD was determined by the investigators at each study site without prespecified diagnostic criteria being provided to the site investigators, rather than through a central review process, so diagnostic variation across institutions was possible.

Disease progression. Among all patients with PPF, FVC declined in both the nintedanib and placebo arms of the INBUILD trial, but the mean annual decline was significantly less (107 ml) in the nintedanib arm. The trial also described “progression of ILD” as an AE without defining it in this context; however, nintedanib decreased the risk of this progression 2.4 times. The difference in the annual decline in FVC between the nintedanib and placebo arms was 128 ml/yr among patients who had a radiological UIP pattern, whereas it was 75.3 ml/yr among patients with a radiological non-UIP pattern (4). Nintedanib decreased the risk of progression of ILD as an AE 2.3 times among patients who had a radiological UIP pattern, but there was no significant difference among patients who had a radiological non-UIP pattern (4).

Patients with PPF who received nintedanib had less annual decline in the FVC if their underlying ILD was CTD-related ILD (106.2 ml/yr less), fibrotic NSIP (141.7 ml/yr less), or fibrotic occupational lung disease (252.8 ml/yr less); however, there was no significant difference in the progression of ILD as an AE for any type of ILD. Among patients with PPF due to fibrotic HP, sarcoidosis, or uILD, there was no difference in the annual decline in FVC or the progression of ILD as an AE. It is noteworthy that the estimates are based on small sample sizes: CTD-related ILD, $n = 147$; fibrotic NSIP, $n = 125$; fibrotic occupational lung disease, $n = 39$; fibrotic HP, $n = 173$; sarcoidosis, $n = 12$; uILD, $n = 114$; and other, $n = 53$ (164).

Mortality. The INBUILD trial showed no significant difference in all-cause mortality or fatal AEs among all patients with PPF. Similarly, there was no difference in all-cause mortality among patients with PPF who had a radiological UIP pattern (4). Mortality was not analyzed among patients with PPF who had a radiological non-UIP pattern (4) or for the type of underlying ILD (164).

Adverse effects. Among all patients with PPF, nintedanib increased gastrointestinal AEs, including abdominal pain (4.2 times), nausea (3.1 times), vomiting (3.6 times), diarrhea (2.8 times), anorexia (2.8 times), weight loss (3.7 times), elevated aspartate aminotransferase (3.2 times), elevated alanine aminotransferase (3.6 times). It also increased the likelihood of any AE (1.1 times), an AE leading to permanent dose reduction (7.9 times), and an AE leading to treatment discontinuation (1.9 times). There were no significant differences in respiratory AEs (including cough, dyspnea, bronchitis, and nasopharyngitis), headache, serious AEs, or severe AEs (4). The finding of more AEs in the nintedanib arm was seen regardless of whether patients had a radiological UIP pattern or non-UIP pattern (4) and regardless of the type of underlying ILD (164), although there was slight variation among groups in which AEs were positive.

Quality of evidence. The quality of evidence for all outcomes was rated as low, meaning that the committee had low confidence in the estimated effects, and therefore, the effects summarized below should be interpreted with caution. The overall low-quality rating is based on the lowest quality of evidence rating among the two critical outcomes; the quality of evidence was moderate for disease progression but low for mortality because there was a single randomized trial with a small number of events, resulting in confidence intervals whose ends included both benefit and harm.

GUIDELINE COMMITTEE CONCLUSIONS.

The decision to make a conditional recommendation for nintedanib in patients with PPF was based on two major factors: 1) there was a statistically significant reduction in disease progression, measured as the annual decline of FVC, and 2) the AEs are reversible with discontinuation of the medication. Of note, the committee acknowledged that the effects of therapy may differ depending on the type of underlying ILD and that management may be based on the underlying ILD in the future; however, for now, there are insufficient data to support such a targeted approach. Therefore, the committee made a research recommendation to investigate the efficacy, effectiveness, and AEs of nintedanib in patients with PPF due to specific types of ILD.

GUIDELINE COMMITTEE VOTE. The committee’s vote was as follows: strong recommendation for nintedanib, 10 of 34 (29%); conditional recommendation for nintedanib, 21 of 34 (62%); conditional recommendation against nintedanib, 0 of 34 (0%); and strong recommendation against nintedanib, 0 of 34 (0%). Three participants (9%) abstained from voting, 1 citing insufficient evidence to make a recommendation and 2 citing insufficient expertise to render a thoughtful judgment.

RESEARCH NEEDS. The existing randomized trial included 663 patients with PPF, but the number of individuals with the various types of ILD that may manifest PPF was small, ranging from only 12 to 173. Limited analyses suggest that there might be differential effects across the different types of ILD. Additional trials are necessary to better quantify treatment effects and identify specific patient populations most likely to benefit from therapy.

Future

Research needs related to antifibrotic therapy in PPF were described above. Additional needs include the following:

- Determine the reasons that a subset of patients with ILD of different etiologies develop a progressive and irreversible fibrotic phenotype in a relatively short time despite initial treatment, including triggers, genetic predisposition, and the role of vascular remodeling (165–167).
- Validate serum biomarkers to identify those at risk of PPF (168, 169), which may be facilitated by proteomic analyses of peripheral blood and BAL fluid (169–171) and transcriptomic studies (170, 172, 173).
- Validate convolutional neural networks (e.g., machine and deep learning algorithms) developed from large HRCT data sets, which may be useful for disease pattern recognition, prognostication, and identifying progression (159, 174–177) and for the characterization of incidentally detected ILAs (176, 178).
- Prioritize research related to the timing and sequence of antifibrotic drugs in relation to corticosteroids and immunosuppressants in the various types of ILD that can manifest PPF.

Conclusions

An international, multidisciplinary committee of experts described radiological and histopathological features of UIP, diagnostic testing for IPF, and treatment of GER in IPF. The committee also defined PPF; described the physiological, radiological, and histopathological

features of PPF; and addressed antifibrotic treatment of PPF. Two specific questions pertaining to the diagnosis of IPF, two specific questions pertaining to the treatment of IPF, and two specific questions pertaining to pharmacotherapy for PPF were answered with evidence-based, graded recommendations. These recommendations are not mandates,

because they cannot account for all unique clinical circumstances, and they should be revisited as new evidence is published. This guideline was reviewed by the ATS Quality Improvement and Implementation Committee; it was determined that none of the recommendations are appropriate targets for performance measures. ■

This official clinical practice guideline was prepared by an *ad hoc* subcommittee of the ATS, ERS, JRS, and ALAT.

Members of the subcommittee are as follows:

GANESH RAGHU, M.D. (Chair)^{1,2,3*}
 MARTINE REMY-JARDIN, M.D., Ph.D. (Co-Chair)^{4†}
 LUCA RICHELDI, M.D., Ph.D. (Co-Chair)^{5‡}
 CAREY C. THOMSON, M.D., M.P.H. (Co-Chair)^{6§}
 KATERINA M. ANTONIOU, M.D., Ph.D.^{7¶}
 BRITTANY D. BISSELL, Pharm.D.^{8,9¶}
 DEMOSTHENES BOUROS, M.D., Ph.D.^{10¶}
 IVETTE BUENDIA-ROLDAN, M.D., Ph.D.^{11**}
 FABIAN CARO, M.D.^{12**}
 BRUNO CRESTANI, M.D., Ph.D.^{13,14¶}
 THOMAS E. WING¹⁵
 MARYA GHAZIPURA, Ph.D., M.S.^{15,16¶¶}
 DERRICK D. HERMAN, M.D.^{17¶}
 LAWRENCE HO, M.D.^{1,2¶¶}
 STEPHANIE M. HON, M.D.^{18¶}
 TANZIB HOSSAIN, M.D., M.S.^{19¶}
 YOSHIKAZU INOUE, M.D., Ph.D.^{20¶¶¶}
 TAKESHI JOHKOH, M.D., Ph.D.^{21¶¶}
 STEPHEN J. ONES^{22††}
 FAYEZ KHEIR, M.D., M.Sc.^{23¶¶¶}
 YETI H. KHOR, M.B. B.S., Ph.D.^{24,25¶}
 SHANDRA L. KNIGHT, M.L.S.^{26¶¶¶}
 MICHAEL KREUTER, M.D.^{27,28¶¶}
 DAVID A. LYNCH, M.B. B.Ch.^{29¶¶¶}
 MADALINA MACREA, M.D., Ph.D.^{30¶}
 TOBY M. MAHER, M.D., Ph.D.^{31,32¶¶¶}
 MANOJ J. MAMMEN, M.D., M.Sc.^{33¶}
 FERNANDO J. MARTINEZ, M.D., M.S.^{34¶¶¶}
 MARIA MOLINA-MOLINA, M.D., Ph.D.^{35¶¶¶}
 JULIE MORISSET, M.D.^{36¶¶}
 JEFFREY L. MYERS, M.D.^{37¶¶¶¶}
 ANDREW G. NICHOLSON, D.M.^{32,38¶¶¶¶}
 AMY L. OLSON, M.D., M.S.P.H.^{39¶¶¶¶}
 ANNA PODOLANCIUK, M.D., M.S.^{34¶¶}
 VENERINO POLETTI, M.D., Ph.D.^{40,41¶}
 CHRISTOPHER J. RYERSON, M.D., M.A.S.^{42¶¶¶}
 MOISE S. SELMAN, M.D.^{43**}
 MARY E. STREK, M.D.^{44¶¶¶}
 LAUREN K. TROY, M.D., Ph.D.^{45¶¶¶}
 MARLIES WUSENBEEK, M.D., Ph.D.^{46¶¶¶}
 KEVIN C. WILSON, M.D.^{47¶}

¹Center for Interstitial Lung Diseases, Division of Pulmonary, Critical Care and Sleep Medicine, ²Department of Medicine, and ³Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington; ⁴Department of Thoracic Imaging, University of Lille, Lille, France; ⁵Division of Pulmonary Medicine, Gemelli University Hospital IRCCS, Rome, Italy; ⁶Department of Medicine, Mount Auburn Hospital/Beth Israel Lahey Health, Harvard Medical School, Cambridge, Massachusetts; ⁷Laboratory of

Molecular and Cellular Pneumology, Department of Respiratory Medicine, School of Medicine, University of Crete, Crete, Greece; ⁸Pharmacy Practice and Science Department, College of Pharmacy, and ⁹Department of Pulmonary, Critical Care, and Sleep, College of Medicine, University of Kentucky, Lexington, Kentucky; ¹⁰Medical School, National and Kapodistrian University of Athens, Athens Medical Center, Athens, Greece; ¹¹National Institute of Respiratory Diseases, The Affiliation Translational Research in Aging and Lung Fibrosis, Mexico City, Mexico; ¹²Interstitial Lung Disease Unit, "Maria Ferrer" Hospital, Buenos Aires, Argentina; ¹³Université de Paris, Inserm 1152, Labex INFLAMEX, Paris, France; ¹⁴Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, Service de pneumologie, Centre de référence constitutif des maladies pulmonaires rares, Paris, France; ¹⁵US

Outcomes Research, New York, New York; ¹⁶Divisions of Epidemiology and Biostatistics, Department of Population Health, New York University Langone Health, New York, New York; ¹⁷Department of Medicine, The Ohio State University, Columbus, Ohio; ¹⁸Department of Medicine, School of Medicine, Tufts University, Boston, Massachusetts; ¹⁹Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Grossman School of Medicine, New York University Langone Health, New York, New York; ²⁰National Hospital Organization Kinki-chuo Chest Medical Center, Osaka, Japan; ²¹Department of Radiology, Kansai Rosai Hospital, Amagasaki, Hyogo Japan; ²²European Idiopathic Pulmonary Fibrosis Federation, Overijse, Belgium; ²³Department of Thoracic Surgery and Interventional Pulmonary, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; ²⁴Department of Respiratory and Sleep Medicine, Austin Health, Heidelberg, Victoria, Australia; ²⁵Faculty of Medicine, University of Melbourne, Melbourne, Victoria, Australia; ²⁶Library and Knowledge Sciences, ²⁷Department of Radiology, and ²⁸Division of Pulmonary and Critical Care Medicine, National Jewish Health, Denver, Colorado; ²⁹Center for Interstitial and Rare Lung Diseases, Department of Pneumology, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; ³⁰German Center for Lung Research, Heidelberg, Germany; ³¹Department of Medicine, Veterans Affairs Medical Center,

Salem, Virginia; ³¹Department of Medicine, Keck School of Medicine of University of Southern California, Los Angeles, California; ³²National Heart and Lung Institute, Imperial College London, London, United Kingdom; ³³Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York; ³⁴Department of Medicine, Joan and Sanford I. Weill Cornell Medicine, New York, New York; ³⁵Interstitial Lung Disease Unit, Respiratory Department, University Hospital of Bellvitge, IDIBELL, University of Barcelona, CIBERES, Barcelona, Spain; ³⁶Département de Médecine, Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada; ³⁷Department of Pathology, Michigan Medicine, Ann Arbor, Michigan; ³⁸Department of Histopathology, Royal Brompton and Harefield Hospitals, London, United Kingdom; ³⁹Department of Diseases of the Thorax, G.B. Morgagni

Hospital, University of Bologna, Forlì, Italy; ⁴⁰Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark; ⁴¹Department of Medicine, University of British Columbia and Centre for Heart Lung Innovation, St. Paul's Hospital, Vancouver, British Columbia, Canada; ⁴²Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas, Mexico City, Mexico; ⁴³Section of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Chicago, Chicago, Illinois; ⁴⁴Centre of Research Excellence in Pulmonary Fibrosis, Royal Prince Alfred Hospital, University of Sydney, Sydney, New South Wales, Australia; ⁴⁵Department of Respiratory Medicine, Centre for Interstitial Lung Diseases and Sarcoidosis, Erasmus University Medical Centre, Rotterdam, the Netherlands; and ⁴⁷Division of Allergy, Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, School of Medicine, Boston University, Boston, Massachusetts

*Co-lead, subcommittee to refine the IPF diagnosis algorithm.

†Co-lead, subcommittee on radiology.

‡Co-lead, subcommittee on physiological criteria for PPF.

¶ERS expert.

¶¶Methodologist.

¶¶¶ALAT expert.

¶¶¶Patient representative.

¶¶¶Co-lead, subcommittee on guideline methodology.

¶¶¶ATS expert.

¶¶¶JRS expert.

***Co-lead, subcommittee to define PPF.

†††Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

§§§Medical librarian.

†††Co-lead, subcommittee on future directions.

****Co-lead, subcommittee on histopathology.

††††Current affiliation: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, Connecticut.

Subcommittee Disclosures: G.R. served on a data safety and monitoring board for Avalyn; received research support from NIH/NHLBI; and served as a consultant for Bellerophon, Biogen, Blade Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Electra Therapeutics, Fibrogen, Nitto, Novartis, Promedior, RespiVant, Roche-Genentech, United Therapeutics, Veracyte, and Zambon. M.R.-J. served on an advisory committee, provided expert testimony, and served as a speaker for Siemens Healthineers; and served as a consultant for Actelion, Boehringer Ingelheim, and LEO Pharma. L.R. served on an advisory committee for Boehringer Ingelheim, CSL Behring, F. Hoffmann La Roche, FibroGen, Nitto, Promedior, and RespiVant; served as a consultant for Acceleron, Asahi Kasei, Biogen Idec, Bristol-Myers Squibb, Celgene, CSL Behring, ImmuneWorks, Nitto, Pliant Therapeutics, RespiVant, Toray Industries, Veracyte, and Zambon; served on a data safety and monitoring board for Celgene; served as a speaker for Boehringer Ingelheim, F. Hoffmann La Roche, and Zambon; and received research support from Boehringer Ingelheim. C.C.T. served on an advisory committee for American College of Radiology and Healthmyne; served as a consultant for American Lung Association and Fulcrum; served as a speaker for American Cancer Society and National Lung Cancer Roundtable; and received royalties from Decision Support Medicine and UpToDate. K.M.A. received research support, travel grants, and honoraria from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Roche. D.B. served on an advisory committee, served as a speaker, and received research support from Boehringer Ingelheim and F. Hoffmann La Roche; received research support from Chiesi Hellas and ELPEN Pharma; and served as a speaker for AstraZeneca and Menarini. B.C. served on an advisory committee for Apellis, AstraZeneca, Boehringer Ingelheim, and Bristol-Myers Squibb; and served as a speaker for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Roche, and Sanofi. M.G. is an employee of ZS Associates. L.H. served as a consultant for Genentech and Roche. Y.I. served on an advisory committee for Asahi Kasei, Boehringer Ingelheim, Galapagos, Roche, Savara, and Taiho; served as a consultant for Boehringer Ingelheim, Promedior, Roche, Savara, and Taiho; served as

a speaker for Boehringer Ingelheim, Kyorin, Shionogi, and Thermo Fisher; and received research support from Japanese Ministry of Health Labor and Welfare and Japan Agency for Medical Research and Development. Y.H.K. served as a speaker for Boehringer Ingelheim and Roche. M.K. served on an advisory committee and received research support from Boehringer Ingelheim and Roche; and served on an advisory committee for Galapagos. D.A.L. served on an advisory committee and speaker for Boehringer Ingelheim; served as a consultant for Calyx, Parexel, and Veracyte; and has a patent issued for "Systems and methods for automatic detection and quantification of pathology using dynamic feature classification." T.M.M. served on an advisory committee for AstraZeneca, Blade Therapeutics, Bristol-Myers Squibb, Boehringer Ingelheim, Galapagos, Galecto, GlaxoSmithKline, IQVIA, Pliant, Roche/Genentech, and Veracyte; served as a consultant for Bristol-Myers Squibb, Boehringer Ingelheim, Galapagos, and Roche; served on a data safety and monitoring board for AstraZeneca, Blade Therapeutics, Celgene, Fibrogen, IQVIA, and United Therapeutics; served as a speaker for Boehringer Ingelheim and Roche; and received research support from AstraZeneca and GlaxoSmithKline. F.J.M. served on an advisory committee for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, DevPro, Gilead, GlaxoSmithKline, IQVIA, Nitto, Novartis, Patara/RespiVant, Polarean, ProMedior/Roche, and Veracyte; served as a consultant for AbbVie, AstraZeneca, Bayer, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, DevPro, Genentech, GlaxoSmithKline, IQVIA, Novartis, Polarean, ProTerra Bio, Pulmatrix, Pulmonx, Raziell, Sanofi, Sanofi/Regeneron, Shionogi, Teva, Theravance/Viatris, twoXAR, United Therapeutics, Veracyte, and Verona; served on a data safety and monitoring board for AbbVie, Biogen, Boehringer Ingelheim, GlaxoSmithKline, and Medtronic; served as a speaker for Academy for Continuing Healthcare Learning, Boehringer Ingelheim, Brooklyn Methodist Hospital, CME Outfitters, France Foundation, GlaxoSmithKline, Integrity Communication, Medscape, NACE/Haymarket, National Association of Managed Care Physicians, Paradigm, PeerView, Physician Education Resource, Projects in Knowledge, United Therapeutics, UpToDate, Vindico, and WebMD/MedScape; received research support from Afferent/Merck, AstraZeneca, Bayer, Biogen, Boehringer Ingelheim, Chiesi, DevPro, Gilead, GlaxoSmithKline, Nitto, Patara/RespiVant, ProMedior/Roche, and Sanofi/Regeneron; and received royalties from UpToDate. M.M.-M. served on an advisory committee for Boehringer Ingelheim, Chiesi, Esteve-Teijin, and Pfizer; served as a speaker for Chiesi and Galapagos; and received research support from Almirall, Boehringer Ingelheim, GlaxoSmithKline, and Roche. J.M. served on

an advisory committee and speaker for Boehringer Ingelheim and F. Hoffmann La Roche. J.L.M. received research support from Veracyte. A.G.N. served as a consultant for Actelion, Boehringer Ingelheim, Galapagos, Medical Quantitative Image Analysis, and Sanofi; and served as a speaker for Boehringer Ingelheim, Roche, and UpToDate. A.L.O. served as a consultant, speaker, and employee of Boehringer Ingelheim (contributions were prior to employment at Boehringer Ingelheim and participation in guideline ceased when employment began); served as a speaker for France Foundation, Genentech, and Peer View; served on an advisory committee for MCG Diagnostics; and received research support from United Therapeutics. A.P. served on an advisory committee for Boehringer Ingelheim; served as a consultant for EBSCO/DynaMed, Imvira, Regeneron, and Roche; served as a speaker for National Association for Continuing Medical Education; and received research support from NHLBI and American Lung Association. V.P. served on an advisory committee and as a speaker for Boehringer Ingelheim; and served as a speaker for ERBE Elektromedizin. C.J.R. served on an advisory committee for AstraZeneca, Boehringer Ingelheim, Cipla, Ensho Health Intelligent Systems, F. Hoffmann La Roche, Pliant Therapeutics, and Veracyte; served as a consultant for Boehringer Ingelheim, F. Hoffmann La Roche, and Veracyte; served as a speaker for AstraZeneca, Boehringer Ingelheim, Cipla, Ensho Health Intelligent Systems, F. Hoffmann La Roche, Pliant Therapeutics, and Veracyte; and received research support from Boehringer Ingelheim, Galapagos, and F. Hoffmann La Roche. M.S. served as a consultant for Boehringer Ingelheim and Celgene. M.E.S. served on an advisory committee for Fibrogen; served as a consultant for, served as a speaker for, and received research support from Boehringer Ingelheim; and received research support from Galapagos and Novartis. L.K.T. received research support from Bayer, Cook Medical, ERBE Elektromedizin, Karl Storz, Medtronic, Olympus, and Rymed; served as a speaker for Boehringer Ingelheim; and served on an advisory committee for Roche. M.W. served on an advisory committee for Boehringer Ingelheim, Bristol-Myers Squibb, Galapagos, F. Hoffmann La Roche, and Novartis; served as a consultant for CLS Behring, Galapagos, Galecto, F. Hoffmann La Roche, Nerre Therapeutics, and RespiVant; served on a data safety and monitoring board for Galapagos and Savara; served as a speaker for Boehringer Ingelheim, Galapagos, and F. Hoffmann La Roche; and received research support from Boehringer Ingelheim, Galapagos, and F. Hoffmann La Roche. K.C.W. is the ATS Chief of Guidelines and Documents, as well as the ATS Documents Editor. B.D.B., I.B.-R., F.C., T.E., D.D.H., S.H., T.H., T.J., S.J., F.K., S.L.K., M.M., and M.J.M. reported no commercial or relevant noncommercial interests.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al.*; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al.*; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:e44–e68.
3. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, *et al.*; American Thoracic Society; European Respiratory Society; Japanese Respiratory Society; Latin American Thoracic Association. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med* 2015;192:e3–e19. [Published erratum appears in *Am J Respir Crit Care Med* 192:644.]
4. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, *et al.*; INBUILD Trial Investigators. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019;381:1718–1727.
5. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ; IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. *Eur Respir J* 2018;51:1800692.
6. Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E; Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical practice guidelines we can trust. Washington, DC: National Academies Press; 2011.
7. Schulzemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, *et al.*; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174:805–814.
8. Galvin JR, Frazier AA, Franks TJ. Collaborative radiologic and histopathologic assessment of fibrotic lung disease. *Radiology* 2010;255:692–706.
9. Leslie KO. Idiopathic pulmonary fibrosis may be a disease of recurrent, tractional injury to the periphery of the aging lung: a unifying hypothesis regarding etiology and pathogenesis. *Arch Pathol Lab Med* 2012;136:591–600.
10. Mai C, Verleden SE, McDonough JE, Willems S, De Wever W, Coolen J, *et al.* Thin-section CT features of idiopathic pulmonary fibrosis correlated with micro-CT and histologic analysis. *Radiology* 2017;283:252–263.
11. Johkoh T, Sumikawa H, Fukuoka J, Tanaka T, Fujimoto K, Takahashi M, *et al.* Do you really know precise radiologic-pathologic correlation of usual interstitial pneumonia? *Eur J Radiol* 2014;83:20–26.
12. Staats P, Kligerman S, Todd N, Tavora F, Xu L, Burke A. A comparative study of honeycombing on high resolution computed tomography with histologic lung remodeling in explants with usual interstitial pneumonia. *Pathol Res Pract* 2015;211:55–61.
13. Picciocchi S, Tomassetti S, Ravaglia C, Gurioli C, Gurioli C, Dubini A, *et al.* From “traction bronchiectasis” to honeycombing in idiopathic pulmonary fibrosis: a spectrum of bronchiolar remodeling also in radiology? *BMC Pulm Med* 2016;16:87.
14. Tominaga J, Bankier AA, Lee KS, Leung AN, Remy-Jardin M, Akira M, *et al.*; Study Group of Diffuse Interstitial Lung Disease in Japan. Interobserver agreement in identifying traction bronchiectasis on computed tomography: its improvement with the use of the additional criteria for chronic fibrosing interstitial pneumonia. *Jpn J Radiol* 2019;37:773–780.
15. Walsh SL, Calandriello L, Sverzellati N, Wells AU, Hansell DM; UIP Observer Consortium. Interobserver agreement for the ATS/ERS/JRS/ALAT criteria for a UIP pattern on CT. *Thorax* 2016;71:45–51.
16. Watanabe T, Sakai F, Johkoh T, Noma S, Akira M, Fujimoto K, *et al.* Interobserver variability in the CT assessment of honeycombing in the lungs. *Radiology* 2013;266:936–944.
17. Lee SI, Chae EJ, Song JS, Lee JH, Song JW. Pleuroparenchymal fibroelastosis in patients with idiopathic pulmonary fibrosis. *Respirology* 2020;25:1046–1052.
18. Oda T, Ogura T, Kitamura H, Hagiwara E, Baba T, Enomoto Y, *et al.* Distinct characteristics of pleuroparenchymal fibroelastosis with usual interstitial pneumonia compared with idiopathic pulmonary fibrosis. *Chest* 2014;146:1248–1255.
19. Fukihara J, Kondoh Y, Brown KK, Kimura T, Kataoka K, Matsuda T, *et al.* Probable usual interstitial pneumonia pattern on chest CT: is it sufficient for a diagnosis of idiopathic pulmonary fibrosis? *Eur Respir J* 2020;55:1802465.
20. Kwon BS, Choe J, Do KH, Hwang HS, Chae EJ, Song JW. Computed tomography patterns predict clinical course of idiopathic pulmonary fibrosis. *Respir Res* 2020;21:295.
21. Raghu G, Wells AU, Nicholson AG, Richeldi L, Flaherty KR, Le Maulf F, *et al.* Effect of nintedanib in subgroups of idiopathic pulmonary fibrosis by diagnostic criteria. *Am J Respir Crit Care Med* 2017;195:78–85.
22. Chung JH, Chawla A, Pelito AL, Cool CD, Groshong SD, Talbert JL, *et al.* CT scan findings of probable usual interstitial pneumonitis have a high predictive value for histologic usual interstitial pneumonitis. *Chest* 2015;147:450–459.
23. Chung JH, Oldham JM, Montner SM, Vij R, Adegunsoye A, Husain AN, *et al.* CT-pathologic correlation of major types of pulmonary fibrosis: implications for revisions to current guidelines. *AJR Am J Roentgenol* 2018;210:1034–1041.
24. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, *et al.* Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society white paper. *Lancet Respir Med* 2018;6:138–153.
25. Raghu G, Remy-Jardin M, Myers J, Richeldi L, Wilson KC. The 2018 diagnosis of idiopathic pulmonary fibrosis guidelines: surgical lung biopsy for radiological pattern of probable usual interstitial pneumonia is not mandatory. *Am J Respir Crit Care Med* 2019;200:1089–1092.
26. Salisbury ML, Tolle LB, Xia M, Murray S, Tayob N, Nambiar AM, *et al.* Possible UIP pattern on high-resolution computed tomography is associated with better survival than definite UIP in IPF patients. *Respir Med* 2017;131:229–235.
27. Brownell R, Moua T, Henry TS, Elicker BM, White D, Vittinghoff E, *et al.* The use of pretest probability increases the value of high-resolution CT in diagnosing usual interstitial pneumonia. *Thorax* 2017;72:424–429.
28. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, *et al.*; Cryobiopsy versus Open Lung Biopsy in the Diagnosis of Interstitial lung Disease Alliance (COLDICE) Investigators. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med* 2020;8:171–181.
29. Cooper WA, Mahar A, Myers JL, Grainge C, Corte TJ, Williamson JP, *et al.* Cryobiopsy for identification of usual interstitial pneumonia and other interstitial lung disease features: further lessons from COLDICE, a prospective multi-center study. *Am J Respir Crit Care Med* 2021;203:1306–1313.
30. Kheir F, Uribe Becerra JP, Bissell B, Ghazipura M, Herman D, Hon SM, *et al.* Transbronchial lung cryobiopsy in patients with interstitial lung disease: a systematic review. *Ann Am Thorac Soc* (In press)
31. Abdelghani R, Thakore S, Kapile U, Lasky JA, Kheir F. Radial endobronchial ultrasound-guided transbronchial cryobiopsy. *J Bronchology Interv Pulmonol* 2019;26:245–249.
32. Aburto M, Peñalva-Izquierdo J, Aguirre U, Barredo I, Echevarria-Uraga JJ, Armendariz K, *et al.* Complications and hospital admission in the following 90 days after lung cryobiopsy performed in interstitial lung disease. *Respir Med* 2020;165:105934.
33. Aragaki-Nakahodo AA, Baughman RP, Shipley RT, Benzaquen S. The complementary role of transbronchial lung cryobiopsy and endobronchial ultrasound fine needle aspiration in the diagnosis of sarcoidosis. *Respir Med* 2017;131:65–69.
34. Bango-Alvarez A, Ariza-Prota M, Torres-Rivas H, Femandez-Femandez L, Prieto A, Sanchez I, *et al.* Transbronchial cryobiopsy in interstitial lung disease: experience in 106 cases—how to do it. *ERJ Open Res* 2017;3:00148–2016.
35. Bondue B, Pieters T, Alexander P, De Vuyst P, Ruiz Patino M, Hoton D, *et al.* Role of transbronchial lung cryobiopsies in diffuse parenchymal lung diseases: interest of a sequential approach. *Pulm Med* 2017;2017:6794343.
36. Camuset J, Naccache JM, Dhalluin X, Febvre M, Wallyn F, Ouenoune O, *et al.* Cryobiopsies trans-bronchiques au cours des pneumopathies

- interstielles diffuses—experiencias preliminares. *Rev Mal Respir* 2019; 38:455–460.
37. Cascante JA, Cebollero P, Herrero S, Yagüe A, Echegoyen A, Elizalde J, *et al.* Transbronchial cryobiopsy in interstitial lung disease: are we on the right path? *J Bronchology Interv Pulmonol* 2016;23:204–209.
 38. Cho R, Zamora F, Gibson H, Dincer HE. Transbronchial lung cryobiopsy in the diagnosis of interstitial lung disease: a retrospective single-center experience. *J Bronchology Interv Pulmonol* 2019;26:15–21.
 39. Cırac AK, Katgi N, Erer OF, Çimen P, Tuksavul FF, Hakoglu B. Diagnostic approach in parenchymal lung diseases: transbronchial lung biopsy or cryobiopsy? *Turk J Med Sci* 2020;50:1535–1539.
 40. Cooley J, Balestra R, Aragaki-Nakahodo AA, Caudell Stamper DN, Sriprasart T, Swank Z, *et al.* Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. *Respir Med* 2018;140:71–76.
 41. Dhooia S, Mehta RM, Srinivasan A, Madan K, Sehgal IS, Pattabhiraman V, *et al.* The safety and efficacy of different methods for obtaining transbronchial lung cryobiopsy in diffuse lung diseases. *Clin Respir J* 2018;12:1711–1720.
 42. Echevarria-Uraga JJ, Peñalva-Izquierdo J, García-Garai N, Gómez-Jimeñez E, Aramburu-Ojembarrera A, Tena-Tudanca L, *et al.* Usefulness of an angioplasty balloon as selective bronchial blockade device after transbronchial cryobiopsy. *Respirology* 2016;21:1094–1099.
 43. Fruchter O, Fridel L, El Raouf BA, Abdel-Rahman N, Rosengarten D, Kramer MR. Histological diagnosis of interstitial lung diseases by cryo-transbronchial biopsy. *Respirology* 2014;19:683–688.
 44. Griff S, Schönfeld N, Ammenwerth W, Blum T-G, Grah C, Bauer TT, *et al.* Diagnostic yield of transbronchial cryobiopsy in non-neoplastic lung disease: a retrospective case series. *BMC Pulm Med* 2014;14:171.
 45. Hagmeyer L, Theegarten D, Tremel M, Priegnitz C, Randerath W. Validation of transbronchial cryobiopsy in interstitial lung disease—interim analysis of a prospective trial and critical review of the literature. *Sarcoidosis Vasculitis Diffuse Lung Dis* 2016;33:2–9.
 46. Hagmeyer L, Theegarten D, Wohlschlagger J, Tremel M, Matthes S, Priegnitz C, *et al.* The role of transbronchial cryobiopsy and surgical lung biopsy in the diagnostic algorithm of interstitial lung disease. *Clin Respir J* 2016;10:589–595.
 47. Hernández-González F, Lucena CM, Ramírez J, Sánchez M, Jiménez MJ, Xaubet A, *et al.* Cryobiopsy in the diagnosis of diffuse interstitial lung disease: yield and cost-effectiveness analysis [in English, Spanish]. *Arch Bronconeumol* 2015;51:261–267.
 48. Hetzel J, Eberhardt R, Petermann C, Gesierich W, Darwiche K, Hagmeyer L, *et al.* Bleeding risk of transbronchial cryobiopsy compared to transbronchial forceps biopsy in interstitial lung disease—a prospective, randomized, multicentre cross-over trial. *Respir Res* 2019; 20:140.
 49. Inomata M, Kuse N, Awano N, Tone M, Yoshimura H, Jo T, *et al.* Prospective multicentre study on the safety and utility of transbronchial lung cryobiopsy with endobronchial balloon. *ERJ Open Res* 2020;6: 00008–2020.
 50. Jacob M, Bastos HN, Mota PC, Melo N, Cunha R, Pereira JM, *et al.* Diagnostic yield and safety of transbronchial cryobiopsy in sarcoidosis. *ERJ Open Res* 2019;5:00203–2019.
 51. Kronborg-White S, Folkersen B, Rasmussen TR, Voldby N, Madsen LB, Rasmussen F, *et al.* Introduction of cryobiopsies in the diagnostics of interstitial lung diseases—experiences in a referral center. *Eur Clin Respir J* 2017;4:1274099.
 52. Kropski JA, Pritchett JM, Mason WR, Sivarajan L, Gleaves LA, Johnson JE, *et al.* Bronchoscopic cryobiopsy for the diagnosis of diffuse parenchymal lung disease. *PLoS One* 2013;8:e78674.
 53. Lentz RJ, Taylor TM, Kropski JA, Sandler KL, Johnson JE, Blackwell TS, *et al.* Utility of flexible bronchoscopic cryobiopsy for diagnosis of diffuse parenchymal lung diseases. *J Bronchology Interv Pulmonol* 2018;25: 88–96.
 54. Linhas R, Marcó A, Oliveira A, Almeida J, Neves S, Campinha S. Transbronchial lung cryobiopsy: associated complications. *Rev Port Pneumol (2006)* 2017;23:331–337.
 55. Pajares V, Puzo C, Castillo D, Lerma E, Montero MA, Ramos-Barboñ D, *et al.* Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology* 2014;19:900–906.
 56. Patrucco F, Daverio M, Gavelli F, Castello L, Boldorini R, Rena O, *et al.* Cryobiopsy in the diagnosis of lung tumors: a single center experience. *Minerva Biotechnol* 2019;31:111–115.
 57. Pourabdollah M, Shamaei M, Karimi S, Karimi M, Kiani A, Jabbari HR. Transbronchial lung biopsy: the pathologist's point of view. *Clin Respir J* 2016;10:211–216.
 58. Ramaswamy A, Homer R, Killam J, Pisani MA, Murphy TE, Araujo K, *et al.* Comparison of transbronchial and cryobiopsies in evaluation of diffuse parenchymal lung disease. *J Bronchology Interv Pulmonol* 2016;23:14–21.
 59. Ravaglia C, Wells AU, Tomassetti S, Gurioli C, Gurioli C, Dubini A, *et al.* Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients. *BMC Pulm Med* 2019;19:16.
 60. Romagnoli M, Colby TV, Berthet J-P, Gamez AS, Mallet J-P, Serre I, *et al.* Poor concordance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung diseases. *Am J Respir Crit Care Med* 2019;199:1249–1256.
 61. Shafiek H, Elbially S, El Achy SN, Gad AYS. Transbronchial cryobiopsy validity in diagnosing diffuse parenchymal lung diseases in Egyptian population. *J Multidiscip Healthc* 2019;12:719–726.
 62. She S, Steinfort DP, Ing AJ, Williamson JP, Leong P, Irving LB, *et al.* Transbronchial cryobiopsy in interstitial lung disease: safety of a standardized procedure. *J Bronchology Interv Pulmonol* 2020;27:36–41.
 63. Sriprasart T, Aragaki A, Baughman R, Wikenheiser-Brokamp K, Khanna G, Tanase D, *et al.* A single US center experience of transbronchial lung cryobiopsy for diagnosing interstitial lung disease with a 2-scope technique. *J Bronchology Interv Pulmonol* 2017;24:131–135.
 64. Tomassetti S, Ravaglia C, Wells AU, Cavazza A, Colby TV, Rossi G, *et al.* Prognostic value of transbronchial lung cryobiopsy for the multidisciplinary diagnosis of idiopathic pulmonary fibrosis: a retrospective validation study. *Lancet Respir Med* 2020;8:786–794.
 65. Tomassetti S, Wells AU, Costabel U, Cavazza A, Colby TV, Rossi G, *et al.* Bronchoscopic lung cryobiopsy increases diagnostic confidence in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2016;193:745–752.
 66. Unterman A, Wand O, Fridel L, Edelstein E, Pertzov B, Kramer MR. High diagnostic accuracy of transbronchial cryobiopsy in fibrotic interstitial lung diseases compared to final explant diagnosis. *Respiration* 2019; 98:421–427.
 67. Ussavarungsi K, Kem RM, Roden AC, Ryu JH, Edell ES. Transbronchial cryobiopsy in diffuse parenchymal lung disease: retrospective analysis of 74 cases. *Chest* 2017;151:400–408.
 68. Wälscher J, Groß B, Eberhardt R, Heussel CP, Eichinger M, Warth A, *et al.* Transbronchial cryobiopsies for diagnosing interstitial lung disease: real-life experience from a tertiary referral center for interstitial lung disease. *Respiration* 2019;97:348–354.
 69. Ravaglia C, Wells AU, Tomassetti S, Dubini A, Cavazza A, Piciocchi S, *et al.* Transbronchial lung cryobiopsy in diffuse parenchymal lung disease: comparison between biopsy from 1 segment and biopsy from 2 segments—diagnostic yield and complications. *Respiration* 2017;93: 285–292.
 70. Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, *et al.* Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the cryobiopsy working group on safety and utility and a call for standardization of the procedure. *Respiration* 2018;95:188–200.
 71. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. *Am J Respir Crit Care Med* 2016;193: 1161–1167.
 72. Lentz RJ, Argento AC, Colby TV, Rickman OB, Maldonado F. Transbronchial cryobiopsy for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. *J Thorac Dis* 2017;9:2186–2203.
 73. Bondue B, Schlossmacher P, Allou N, Gazaille V, Taton O, Gevenois PA, *et al.* Trans-bronchial lung cryobiopsy in patients at high-risk of complications. *BMC Pulm Med* 2021;21:135.
 74. Kim SY, Diggins J, Pankratz D, Huang J, Pagan M, Sindy N, *et al.* Classification of usual interstitial pneumonia in patients with interstitial lung disease: assessment of a machine learning approach using high-dimensional transcriptional data. *Lancet Respir Med* 2015;3:473–482.

75. Raghu G, Flaherty KR, Lederer DJ, Lynch DA, Colby TV, Myers JL, *et al.* Use of a molecular classifier to identify usual interstitial pneumonia in conventional transbronchial lung biopsy samples: a prospective validation study. *Lancet Respir Med* 2019;7:487–498.
76. Kheir F, Uribe Becerra JP, Bissell B, Ghazipura M, Herman D, Hon SM, *et al.* Use of a genomic classifier in patients with interstitial lung disease: a systematic review. *Ann Am Thorac Soc* [online ahead of print] 2 Jun 2021; DOI: 10.1513/AnnalsATS.202102-197OC.
77. Kheir F, Alkhatib A, Berry GJ, Daroca P, Diethelm L, Rampolla R, *et al.* Using bronchoscopic lung cryobiopsy and a genomic classifier in the multidisciplinary diagnosis of diffuse interstitial lung diseases. *Chest* 2020;158:2015–2025.
78. Pankratz DG, Choi Y, Imitiaz U, Fedorowicz GM, Anderson JD, Colby TV, *et al.* Usual interstitial pneumonia can be detected in transbronchial biopsies using machine learning. *Ann Am Thorac Soc* 2017;14:1646–1654.
79. Richeldi L, Scholander MB, Lynch DA, Colby TV, Myers JL, Groshong SD, *et al.* Utility of a molecular classifier as a complement to high-resolution computed tomography to identify usual interstitial pneumonia. *Am J Respir Crit Care Med* 2021;203:211–220.
80. Raghu G, Freudenberger TD, Yang S, Curtis JR, Spada C, Hayes J, *et al.* High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. *Eur Respir J* 2006;27:136–142.
81. Tobin RW, Pope CE II, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;158:1804–1808.
82. Tossier C, Dupin C, Plantier L, Leger J, Flament T, Favelle O, *et al.* Hiatal hernia on thoracic computed tomography in pulmonary fibrosis. *Eur Respir J* 2016;48:833–842.
83. Lee JS, Ryu JH, Elicker BM, Lydell CP, Jones KD, Wolters PJ, *et al.* Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;184:1390–1394.
84. Lee JS, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, *et al.* IPFnet Investigators. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. *Lancet Respir Med* 2013;1:369–376.
85. Khor YHBB, Ghazipura M, Herman D, Hon SM, Hossain T, Kheir F, *et al.* Antacid medication and anti-reflux surgery in patients with idiopathic pulmonary fibrosis: a systematic review. *Ann Am Thorac Soc* (In press)
86. Dutta P, Funston W, Mossop H, Ryan V, Jones R, Forbes R, *et al.* Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax* 2019;74:346–353.
87. Costabel U, Behr J, Crestani B, Stansen W, Schlenker-Herzog R, Stowasser S, *et al.* Anti-acid therapy in idiopathic pulmonary fibrosis: insights from the INPULSIS trials. *Respir Res* 2018;19:167.
88. Ghebremariam YT, Cooke JP, Gerhart W, Griego C, Brower JB, Doyle-Eisele M, *et al.* Pleiotropic effect of the proton pump inhibitor esomeprazole leading to suppression of lung inflammation and fibrosis. *J Transl Med* 2015;13:249.
89. Jo HE, Corte TJ, Glaspole I, Grainge C, Hopkins PMA, Moodley Y, *et al.* Gastroesophageal reflux and antacid therapy in IPF: analysis from the Australia IPF Registry. *BMC Pulm Med* 2019;19:84.
90. Kreuter M, Ehlers-Tenenbaum S, Palmowski K, Bruhwiler J, Oltmanns U, Muley T, *et al.* Impact of comorbidities on mortality in patients with idiopathic pulmonary fibrosis. *PLoS One* 2016;11:e0151425.
91. Kreuter M, Spagnolo P, Wuyts W, Renzoni E, Koschel D, Bonella F, *et al.* Antacid therapy and disease progression in patients with idiopathic pulmonary fibrosis who received pirfenidone. *Respiration* 2017;93:415–423.
92. Kreuter M, Wuyts W, Renzoni E, Koschel D, Maher TM, Kolb M, *et al.* Antacid therapy and disease outcomes in idiopathic pulmonary fibrosis: a pooled analysis. *Lancet Respir Med* 2016;4:381–389.
93. Lee CM, Lee DH, Ahn BK, Hwang JJ, Yoon H, Shin CM, *et al.* Protective effect of proton pump inhibitor for survival in patients with gastroesophageal reflux disease and idiopathic pulmonary fibrosis. *J Neurogastroenterol Motil* 2016;22:444–451.
94. Liu B, Su F, Xu N, Qu T, Li M, Ju Y. Chronic use of anti-reflux therapy improves survival of patients with pulmonary fibrosis. *Int J Clin Exp Med* 2017;10:5805–5810.
95. Tran T, Assayag D, Ernst P, Suissa S. Effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis: a population-based cohort study. *Chest* 2021;159:673–682.
96. Umeda T, Webber B, Tomic R, Brown R, Rudser K, Kim H, *et al.* Impact of antacid therapy on transplant free survival of patients with idiopathic pulmonary fibrosis [abstract]. *Am J Respir Crit Care Med* 2018;199:A4256.
97. Kilduff CE, Counter MJ, Thomas GA, Harrison NK, Hope-Gill BD. Effect of acid suppression therapy on gastroesophageal reflux and cough in idiopathic pulmonary fibrosis: an intervention study. *Cough* 2014;10:4.
98. Raghu G, Pellegrini CA, Yow E, Flaherty KR, Meyer K, Noth I, *et al.* Laparoscopic anti-reflux surgery for the treatment of idiopathic pulmonary fibrosis (WRAP-IPF): a multicentre, randomised, controlled phase 2 trial. *Lancet Respir Med* 2018;6:707–714.
99. Linden PA, Gilbert RJ, Yeap BY, Boyle K, Deykin A, Jaklitsch MT, *et al.* Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation. *J Thorac Cardiovasc Surg* 2006;131:438–446.
100. Raghu G, Morrow E, Collins BF, Ho LA, Hinojosa MW, Hayes JM, *et al.* Laparoscopic anti-reflux surgery for idiopathic pulmonary fibrosis at a single centre. *Eur Respir J* 2016;48:826–832.
101. Cutting CC, Bowman WS, Dao N, Pugashetti JV, Garcia CK, Oldham JM, *et al.* Family history of pulmonary fibrosis predicts worse survival in patients with interstitial lung disease. *Chest* 2021;159:1913–1921.
102. Garc  a-Sancho C, Buend  a-Rold  n I, Fern  ndez-Plata MR, Navarro C, Pe  rez-Padilla R, Vargas MH, *et al.* Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. *Respir Med* 2011;105:1902–1907.
103. Hunninghake GM, Quesada-Arias LD, Carmichael NE, Martinez Manzano JM, Poli De Fr  as S, Baumgartner MA, *et al.* Interstitial lung disease in relatives of patients with pulmonary fibrosis. *Am J Respir Crit Care Med* 2020;201:1240–1248.
104. Krauss E, Gehrken G, Drakopanagiotakis F, Tello S, Dartsch RC, Maurer O, *et al.* Clinical characteristics of patients with familial idiopathic pulmonary fibrosis (f-IPF). *BMC Pulm Med* 2019;19:130.
105. Planas-Cerezales L, Arias-Salgado EG, Buend  a-Rold  n I, Montes-Worboys A, Lo  pez CE, Vicens-Zygmunt V, *et al.* Predictive factors and prognostic effect of telomere shortening in pulmonary fibrosis. *Respirology* 2019;24:146–153.
106. Salisbury ML, Hewlett JC, Ding G, Markin CR, Douglas K, Mason W, *et al.* Development and progression of radiologic abnormalities in individuals at risk for familial interstitial lung disease. *Am J Respir Crit Care Med* 2020;201:1230–1239.
107. Hewitt RJ, Maher TM. Idiopathic pulmonary fibrosis: new and emerging treatment options. *Drugs Aging* 2019;36:485–492.
108. Hirani N, MacKinnon AC, Nicol L, Ford P, Schambye H, Pedersen A, *et al.* Target inhibition of galectin-3 by inhaled TD139 in patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2021;57:2002559.
109. Raghu G, van den Blink B, Hamblin MJ, Brown AW, Golden JA, Ho LA, *et al.* Effect of recombinant human pentraxin 2 vs placebo on change in forced vital capacity in patients with idiopathic pulmonary fibrosis: a randomized clinical trial. *JAMA* 2018;319:2299–2307.
110. Spagnolo P, Bonella F, Ryerson CJ, Tzouveleakis A, Maher TM. Shedding light on developmental drugs for idiopathic pulmonary fibrosis. *Expert Opin Investig Drugs* 2020;29:797–808.
111. Trachalaki A, Irfan M, Wells AU. Pharmacological management of idiopathic pulmonary fibrosis: current and emerging options. *Expert Opin Pharmacother* 2021;22:191–204.
112. Richeldi L, Fern  ndez Pe  rez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, *et al.* Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2020;8:25–33.
113. Holland AE, Corte T, Chambers DC, Palmer AJ, Ekstro  m MP, Glaspole I, *et al.* Ambulatory oxygen for treatment of exertional hypoxaemia in pulmonary fibrosis (PFOX trial): a randomised controlled trial. *BMJ Open* 2020;10:e040798.
114. Kahlmann V, Moor CC, Wijsenbeek MS. Managing fatigue in patients with interstitial lung disease. *Chest* 2020;158:2026–2033.
115. Kreuter M, Bendstrup E, Russell A-M, Bajwah S, Lindell K, Adir Y, *et al.* Palliative care in interstitial lung disease: living well. *Lancet Respir Med* 2017;5:988–980.

116. Lindell K, Raghu G. Palliative care for patients with pulmonary fibrosis: symptom relief is essential. *Eur Respir J* 2018;52:1802088.
117. Lindell KO, Nouraei M, Klesen MJ, Klein S, Gibson KF, Kass DJ, et al. Randomised clinical trial of an early palliative care intervention (SUPPORT) for patients with idiopathic pulmonary fibrosis (IPF) and their caregivers: protocol and key design considerations. *BMJ Open Respir Res* 2018;5:e000272.
118. Moor CC, Wijsenbeek MS, Balestro E, Biondini D, Bondue B, Cottin V, et al. Gaps in care of patients living with pulmonary fibrosis: a joint patient and expert statement on the results of a Europe-wide survey. *ERJ Open Res* 2019;5:00124-2019.
119. Perez-Bogerd S, Wuyts W, Barbier V, Demeyer H, Van Muylen A, Janssens W, et al. Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. *Respir Res* 2018;19:182.
120. Somogyi V, Chaudhuri N, Torrisi SE, Kahn N, Müller V, Kreuter M. The therapy of idiopathic pulmonary fibrosis: what is next? *Eur Respir Rev* 2019;28:190021.
121. Torrisi SE, Ley B, Kreuter M, Wijsenbeek M, Vittinghoff E, Collard HR, et al. The added value of comorbidities in predicting survival in idiopathic pulmonary fibrosis: a multicentre observational study. *Eur Respir J* 2019;53:1801587.
122. Whitty JA, Rankin J, Visca D, Tsipouri V, Mori L, Spencer L, et al. Cost-effectiveness of ambulatory oxygen in improving quality of life in fibrotic lung disease: preliminary evidence from the AmbOx trial. *Eur Respir J* 2020;55:1901157.
123. Wijsenbeek MS, Holland AE, Swigris JJ, Renzoni EA. Comprehensive supportive care for patients with fibrosing interstitial lung disease. *Am J Respir Crit Care Med* 2019;200:152–159.
124. Brown KK, Martinez FJ, Walsh SL, Thannickal VJ, Prasse A, Schlenker-Herzog R, et al. The natural history of progressive fibrosing interstitial lung diseases. *Eur Respir J* 2020;55:2000085.
125. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis—FDA review of pirfenidone and nintedanib. *N Engl J Med* 2015;372:1189–1191.
126. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med* 2011;184:1382–1389.
127. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F, et al. RELIEF Investigators. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021;9:476–486.
128. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2020;8:147–157.
129. Kreuter M, Kahn N, Sambataro FM, Heussel C, Sambataro G, Vancheri C, et al. To be or not to be—the uncertainty of PF-ILD. *Eur Respir J* 2020;56:3713.
130. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:538–542.
131. Ryerson CJ, Urbania TH, Richeldi L, Mooney JJ, Lee JS, Jones KD, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. *Eur Respir J* 2013;42:750–757.
132. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis: an international working group report. *Am J Respir Crit Care Med* 2016;194:285–275.
133. Akira M, Inoue Y, Arai T, Okuma T, Kawata Y. Long-term follow-up high-resolution CT findings in non-specific interstitial pneumonia. *Thorax* 2011;66:61–65.
134. Lee HY, Lee KS, Jeong YJ, Hwang JH, Kim HJ, Chung MP, et al. High-resolution CT findings in fibrotic idiopathic interstitial pneumonias with little honeycombing: serial changes and prognostic implications. *AJR Am J Roentgenol* 2012;199:982–989.
135. Yamauchi H, Bando M, Baba T, Kataoka K, Yamada Y, Yamamoto H, et al. Clinical course and changes in high-resolution computed tomography findings in patients with idiopathic pulmonary fibrosis without honeycombing. *PLoS One* 2016;11:e0166168.
136. Jacob J, Aksman L, Mogulkoc N, Procter AJ, Gholipour B, Cross G, et al. Serial CT analysis in idiopathic pulmonary fibrosis: comparison of visual features that determine patient outcome. *Thorax* 2020;75:648–654.
137. Silva CIS, Müller NL, Hansell DM, Lee KS, Nicholson AG, Wells AU. Nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis: changes in pattern and distribution of disease over time. *Radiology* 2008;247:251–259.
138. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of hypersensitivity pneumonitis in adults: an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020;202:e36–e69.
139. Salisbury ML, Gross BH, Chughtai A, Sayyoun M, Kazerooni EA, Bartholmai BJ, et al. Development and validation of a radiological diagnosis model for hypersensitivity pneumonitis. *Eur Respir J* 2018;52:1800443.
140. Carnevale A, Silva M, Maietti E, Milanese G, Saracco M, Parisi S, et al. Longitudinal change during follow-up of systemic sclerosis: correlation between high-resolution computed tomography and pulmonary function tests. *Clin Rheumatol* 2021;40:213–219.
141. Kolb M, Vasakova M. The natural history of progressive fibrosing interstitial lung diseases. *Respir Res* 2019;20:57.
142. Putman RK, Gudmundsson G, Axelsson GT, Hida T, Honda O, Araki T, et al. Imaging patterns are associated with interstitial lung abnormality progression and mortality. *Am J Respir Crit Care Med* 2019;200:175–183.
143. Hatabu H, Hunninghake GM, Lynch DA. Interstitial lung abnormality: recognition and perspectives. *Radiology* 2019;291:1–3.
144. Hansell DM, Goldin JG, King TE Jr, Lynch DA, Richeldi L, Wells AU. CT staging and monitoring of fibrotic interstitial lung diseases in clinical practice and treatment trials: a position paper from the Fleischner Society. *Lancet Respir Med* 2015;3:483–496.
145. Wu X, Kim GH, Salisbury ML, Barber D, Bartholmai BJ, Brown KK, et al. Computed tomographic biomarkers in idiopathic pulmonary fibrosis: the future of quantitative analysis. *Am J Respir Crit Care Med* 2019;199:12–21.
146. Best AC, Lynch AM, Bozic CM, Miller D, Grunwald GK, Lynch DA. Quantitative CT indexes in idiopathic pulmonary fibrosis: relationship with physiologic impairment. *Radiology* 2003;228:407–414.
147. Best AC, Meng J, Lynch AM, Bozic CM, Miller D, Grunwald GK, et al. Idiopathic pulmonary fibrosis: physiologic tests, quantitative CT indexes, and CT visual scores as predictors of mortality. *Radiology* 2008;246:935–940.
148. Khanna D, Nagaraja V, Tseng CH, Abtin F, Suh R, Kim G, et al. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials. *Arthritis Res Ther* 2015;17:372.
149. Kim HJ, Brown MS, Chong D, Gjertson DW, Lu P, Kim HJ, et al. Comparison of the quantitative CT imaging biomarkers of idiopathic pulmonary fibrosis at baseline and early change with an interval of 7 months. *Acad Radiol* 2015;22:70–80.
150. Kim HJ, Brown MS, Elashoff R, Li G, Gjertson DW, Lynch DA, et al. Quantitative texture-based assessment of one-year changes in fibrotic reticular patterns on HRCT in scleroderma lung disease treated with oral cyclophosphamide. *Eur Radiol* 2011;21:2455–2465.
151. Kim HJ, Li G, Gjertson D, Elashoff R, Shah SK, Ochs R, et al. Classification of parenchymal abnormality in scleroderma lung using a novel approach to denoise images collected via a multicenter study. *Acad Radiol* 2008;15:1004–1016.
152. Salisbury ML, Lynch DA, van Beek EJ, Kazerooni EA, Guo J, Xia M, et al. IPFNet Investigators. Idiopathic pulmonary fibrosis: the association between the adaptive multiple features method and fibrosis outcomes. *Am J Respir Crit Care Med* 2017;195:921–929.
153. Iwasawa T, Ogura T, Sakai F, Kanauchi T, Komagata T, Baba T, et al. CT analysis of the effect of pirfenidone in patients with idiopathic pulmonary fibrosis. *Eur J Radiol* 2014;83:32–38.
154. Jacob J, Bartholmai BJ, Egashira R, Brun AL, Rajagopalan S, Karwowski R, et al. Chronic hypersensitivity pneumonitis: identification of key prognostic determinants using automated CT analysis. *BMC Pulm Med* 2017;17:81.

155. Jacob J, Bartholmai BJ, Rajagopalan S, Egashira R, Brun AL, Kokosi M, *et al*. Unclassifiable-interstitial lung disease: outcome prediction using CT and functional indices. *Respir Med* 2017;130:43–51.
156. Jacob J, Bartholmai BJ, Rajagopalan S, Karwoski R, Walsh SLF, *et al*. Likelihood of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and emphysema. *Respirology* 2018;23:593–599.
157. Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Nair A, Karwoski R, *et al*. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. *Eur Respir J* 2017;49:1601011.
158. Jacob J, Bartholmai BJ, Rajagopalan S, van Moersel CHM, van Es HW, van Beek FT, *et al*. Predicting outcomes in idiopathic pulmonary fibrosis using automated computed tomographic analysis. *Am J Respir Crit Care Med* 2018;198:767–776.
159. Humphries SM, Swigors JJ, Brown KK, Strand M, Gong Q, Sundry JS, *et al*. Quantitative high-resolution computed tomography fibrosis score: performance characteristics in idiopathic pulmonary fibrosis. *Eur Respir J* 2018;52:1801384.
160. Humphries SM, Yagihashi K, Huckleberry J, Rho B-H, Schroeder JD, Strand M, *et al*. Idiopathic pulmonary fibrosis: data-driven textural analysis of extent of fibrosis at baseline and 15-month follow-up. *Radiology* 2017;285:270–278.
161. Mathai SK, Humphries S, Kropski JA, Blackwell TS, Powers J, Walts AD, *et al*. MUC5B variant is associated with visually and quantitatively detected preclinical pulmonary fibrosis. *Thorax* 2019;74:1131–1139.
162. Ghazipura MHT, Mammen MJ, Bissell B, Macrea M, Herman D, Hon SM, *et al*. Pirfenidone in progressive pulmonary fibrosis. *Ann Am Thorac Soc* (In press).
163. Ghazipura MHM, Mammen MJ, Herman DD, Hon SM, Bissell BD, Macrea M, *et al*. Nintedanib in progressive pulmonary fibrosis. *Ann Am Thorac Soc* (In press).
164. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, *et al*. INBUILD trial investigators. Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med* 2020;8:453–460.
165. Selman M, Pardo A. When things go wrong: exploring possible mechanisms driving the progressive fibrosis phenotype in interstitial lung diseases. *Eur Respir J* 2021;58:2004507.
166. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, *et al*. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021;384:325–334.
167. Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. *N Engl J Med* 2020;383:958–968.
168. Moodley YP, Corte TJ, Oliver BG, Glaspole IN, Livk A, Ito J, *et al*. Analysis by proteomics reveals unique circulatory proteins in idiopathic pulmonary fibrosis. *Respirology* 2019;24:1111–1114.
169. Todd JL, Neely ML, Overton R, Durham K, Gulati M, Huang H, *et al*. IPF-PRO Registry investigators. Peripheral blood proteomic profiling of idiopathic pulmonary fibrosis biomarkers in the multicentre IPF-PRO Registry. *Respir Res* 2019;20:227.
170. Herazo-Maya JD, Sun J, Molyneaux PL, Li Q, Villalba JA, Tzouvelekas A, *et al*. Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study. *Lancet Respir Med* 2017;5:857–868.
171. Landi C, Bargagli E, Bianchi L, Gagliardi A, Carleo A, Bennett D, *et al*. Towards a functional proteomics approach to the comprehension of idiopathic pulmonary fibrosis, sarcoidosis, systemic sclerosis and pulmonary Langerhans cell histiocytosis. *J Proteomics* 2013;83:60–75.
172. Habermann AC, Gutierrez AJ, Bui LT, Yahn SL, Winters NI, Calvi CL, Peter L, Chung M-I, Taylor CJ, Jetter C. Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. *Sci Adv* 2020;6:eaba1972.
173. Reyfman PA, Walter JM, Joshi N, Anekalla KR, McQuattie-Pimentel AC, Chiu S, *et al*. Single-cell transcriptomic analysis of human lung provides insights into the pathobiology of pulmonary fibrosis. *Am J Respir Crit Care Med* 2019;199:1517–1536.
174. Gao M, Bagci U, Lu L, Wu A, Buty M, Shin H-C, *et al*. Holistic classification of CT attenuation patterns for interstitial lung diseases via deep convolutional neural networks. *Comput Methods Biomech Biomed Eng Imaging Vis* 2018;6:1–6.
175. Walsh SLF, Calandriello L, Silva M, Sverzellati N. Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: a case-cohort study. *Lancet Respir Med* 2018;6:837–845.
176. Walsh SLF, Humphries SM, Wells AU, Brown KK. Imaging research in fibrotic lung disease: applying deep learning to unsolved problems. *Lancet Respir Med* 2020;8:1144–1153.
177. Wang C, Moriya T, Hayashi Y, Roth H, Lu L, Oda M, *et al*. Weakly-supervised deep learning of interstitial lung disease types on CT images. In: Mori K, Hahn HK, editors. Medical imaging 2019: computer-aided diagnosis. Bellingham, WA: International Society for Optics and Photonics; 2019. p. 109501H.
178. Bermejo-Pelaez D, Ash SY, Washko GR, San Jose Estelupar R, Ledesma-Carbajo MJ. Classification of interstitial lung abnormality patterns with an ensemble of deep convolutional neural networks. *Sci Rep* 2020;10:338.
179. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, *et al*. ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013;188:733–748.
180. Khirya R, Macaluso C, Montero M, Wells AU, Chua F, Kokosi M, *et al*. Pleuroparenchymal fibroelastosis: a review of histopathological features and the relationship between histologic parameters and survival. *Am J Surg Pathol* 2017;41:1683–1689.
181. Yousem SA. Cicatricial variant of cryptogenic organizing pneumonia. *Hum Pathol* 2017;64:76–82.
182. Beardsley B, Rassi D. Fibrosing organising pneumonia. *J Clin Pathol* 2013;66:875–881.
183. Roggli VL, Gibbs AR, Attanoos R, Chung A, Popper H, Cagle P, *et al*. Pathology of asbestosis—an update of the diagnostic criteria: report of the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society. *Arch Pathol Lab Med* 2010;134:462–480.
184. Larsen BT, Smith ML, Elicker BM, Fernandez JM, de Morvil GAA, Pereira CAC, *et al*. Diagnostic approach to advanced fibrotic interstitial lung disease: bringing together clinical, radiologic, and histologic clues. *Arch Pathol Lab Med* 2017;141:901–915.
185. Zhang C, Chan KM, Schmidt LA, Myers JL. Histopathology of explanted lungs from patients with a diagnosis of pulmonary sarcoidosis. *Chest* 2016;149:499–507.