CLINICAL STUDY PROTOCOL

A DOUBLE-BLIND, RANDOMISED, PLACEBO CONTROLLED, TWO PERIOD CROSS-OVER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ORVEPITANT IN CHRONIC COUGH IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

Short Study Title:	Phase 2 Efficacy and Safety Study of Orvepitant for Chronic Cough in Patients with IPF
IND No:	132343
EudraCT No:	2021-006278-22
Protocol No. / Name:	ORV-PF-01 / IPF COMFORT
Version No:	Final V4.0 (US)
Date of Protocol:	16 May 2024

Sponsor:

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Confidentiality Statement:

This protocol contains information which is the property of NeRRe Therapeutics Ltd and therefore is provided to you in confidence for review by you, your staff, an applicable ethics committee/institutional review board and regulatory authorities. It is understood that this information will not be disclosed to others without the written approval from NeRRe Therapeutics Ltd.

This study will be conducted in compliance with Good Clinical Practice (GCP), the General Principles of the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

1. PROTOCOL SYNOPSIS

Protocol Title	A DOUBLE-BLIND, RANDOMISED, PLACEBO CONTROLLED, TWO PERIOD CROSS-OVER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ORVEPITANT IN CHRONIC COUGH IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS
SHORT PROTOCOL TITLE	Phase 2 Efficacy and Safety Study of Orvepitant for Chronic Cough in Patients with IPF
PROTOCOL No. / Name	ORV-PF-01 / IPF COMFORT
CHIEF INVESTIGATOR	[redacted]
SPONSOR	NeRRe Therapeutics Ltd
INVESTIGATIONAL MEDICINAL PRODUCT	Orvepitant and placebo
PHASE OF DEVELOPMENT	Phase 2
INDICATION	Chronic cough associated with idiopathic pulmonary fibrosis
STUDY DESIGN	The study will be a multi-center, double-blind, randomised, placebo-controlled 2-period cross-over study in subjects with chronic cough due to idiopathic pulmonary fibrosis (IPF). Subjects will participate in one of two cohorts (Cohort 1 and Cohort 2). Cohort 1 will evaluate a 30 mg orvepitant dose and Cohort 2 the 10 mg dose. Within each cohort, subjects will be randomised to receive either orvepitant or placebo in the first treatment period (Treatment Period A) followed by the alternate treatment in Treatment Period B. There will be a wash-out period of 3 weeks between the two treatment periods. Subjects will be randomised 1:1 to each of the two treatment orders and 1:1 to each cohort.

	Subjects will enter a screening period of between 14 and 28 days to determine eligibility. Eligible subjects will be randomised at the Baseline visit and will participate in two identical 28 day treatment periods with the wash-out period between them. There will be a total of 8 visits including the Screening, Baseline and final Follow-up visits.

STUDY OBJECTIVES	
Primary	• To evaluate the effect of orvepitant once daily on cough severity, as perceived by patients, with IPF • To evaluate the safety of orvepitant once daily in patients with IPF
Secondary	• To evaluate the effect of orvepitant once daily on other measures of cough burden and on health-related quality of life in patients with IPF • To evaluate the effect of orvepitant on other comorbidities in patients with IPF
Exploratory	• To evaluate the effect of orvepitant once daily on markers of disease activity in patients with IPF • To evaluate the relationship between plasma concentrations of orvepitant and efficacy in patients with IPF
EFFICACY ASSESSMENTS AND ENDPOINTS	
EFFICACY ASSESSMENTS	EFFICACY ENDPOINTS
IPF Coughing Severity Scale completed daily from Screening to Week 4 of Treatment Period B	**Primary Efficacy Endpoint** • Mean change from Baseline to Week 4 (the last 7 days of treatment) in weekly average of the daily IPF Coughing Severity Scale **Secondary efficacy endpoints** • Mean change from Baseline to Week 2 in weekly average of the daily IPF Coughing Severity Scale
Additional cough severity scales Early morning and rest of the day cough scales, completed daily from Screening to Week 4 of Treatment Period B	**Secondary efficacy endpoints** • Mean change from Baseline to Weeks 2 and 4 in weekly average of the early morning cough scale • Mean change from Baseline to Weeks 2 and 4 in weekly average of the rest of the day cough scale

Urge to cough scale completed daily from Screening to Week 4 of Treatment Period B	**Secondary efficacy endpoints** • Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily urge to cough scale
Cough frequency scale completed daily from Screening to Week 4 of Treatment Period B	**Secondary efficacy endpoints** • Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily cough frequency scale
Dyspnoea scale completed daily from Screening to Week 4 of Treatment Period B	**Secondary efficacy endpoints** • Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily dyspnoea scale
Patient global ratings of cough severity for all coughing, early morning coughing and rest of the day coughing, each measured using a 5-point categorical rating scale completed at all visits except Screening	**Secondary efficacy endpoints** • Proportion of subjects in each category at Weeks 2 and 4 for each global rating of cough
Patient global ratings of change in cough severity for all coughing, early morning coughing and rest of the day coughing, each measured using a 7-point rating scale completed at all visits except Screening and Baseline	**Secondary efficacy endpoints** • Proportion of subjects in each category at Weeks 2 and 4 for each global rating of cough
Cough frequency measured using the Leicester Cough Monitor ambulatory cough monitor applied for 24-hours at Baseline and in Week 4 of each treatment period	**Secondary efficacy endpoints** • Mean change from Baseline to Week 4 in 24-hour cough frequency • Mean change from Baseline to Week 4 in awake cough frequency • Mean change from Baseline to Week 4 in night-time cough frequency • Mean change from Baseline to Week 4 in the number of coughing bouts
Leicester Cough Questionnaire (LCQ) completed at Baseline, End of Wash-out and Week 4 of each treatment period	**Secondary efficacy endpoints** • Mean change from Baseline to Week 4 in LCQ total and domain (Physical, Social, Psychological) scores
King's Brief Interstitial Lung Disease health status questionnaire (K-BILD) completed at Baseline, End of Wash-out and Week 4 of each treatment period	**Secondary efficacy endpoints** • Mean change from Baseline to Week 4 in K-BILD total and domain (Psychological, Breathlessness, Chest Symptoms) scores • Proportion of patients with a clinically relevant improvement in total K-BILD score
PROMIS SF SD 8b sleep assessment questionnaire completed	**Secondary efficacy endpoints** • Mean change from Baseline to Week 4 in the PROMIS SF SD 8b score

at Baseline, End of Wash-out and Week 4 of each treatment period	
Hospital Anxiety and Depression Scale (HADS) questionnaire completed at Baseline, End of Wash-out and Week 4 of each treatment period	**Secondary efficacy endpoints** • Mean change from Baseline to Week 4 in the HADS score
Hull Airway Reflux Questionnaire (HARQ) completed at Baseline and in Week 4 of each treatment period	**Secondary efficacy endpoints** • Mean change from Baseline to Week 4 in the HARQ score
SAFETY ASSESSMENTS AND ENDPOINTS	
SAFETY ASSESSMENTS	SAFETY ENDPOINTS
Pulmonary function tests measured in the clinic at: • Screening, Baseline, End of Wash-out, Week 4 of each treatment period and Follow-up.	• Change from Baseline in forced vital capacity (FVC), forced expired volume in one second (FEV1), peak expiratory flow rate and vital capacity (VC)
Adverse events recorded throughout the study (from Screening Visit to the Follow-Up Visit)	• Number of treatment emergent adverse events • Number of treatment emergent serious adverse events • Number of treatment emergent adverse events resulting in treatment discontinuation • Severity of treatment emergent adverse events • Number of treatment emergent related adverse events
Physical Examination recorded: • At Screening, Baseline and Follow-up.	• Treatment emergent changes in physical examination will be recorded as adverse events
Vital Signs (pulse rate, systolic and diastolic blood pressure, temperature, arterial oxygen saturation) recorded: • At Screening, Baseline, End of Wash-out, Week 4 of each treatment period and Follow-up. Additionally, weight recorded: • At Baseline and Follow-up.	• Mean change from Baseline in each vital sign: - Systolic blood pressure - Diastolic blood pressure - Pulse rate - Temperature - Arterial oxygen saturation - Weight • Note: Clinically significant changes in vital signs are recorded as adverse events

Haematology, clinical chemistry and urinalysis parameters in samples collected: • At Screening, Baseline, End of Wash-out, Week 4 of each treatment period and Follow-up.	• Mean change from Baseline in each haematology parameter • Mean change from Baseline in each clinical chemistry parameter • Shift from Baseline in each urinalysis parameter • Note: clinically significant changes in laboratory parameters are recorded as adverse events
12-lead ECG, recorded: • At Screening, Baseline, End of Wash-out, Week 4 of each treatment period and Follow-up.	• Proportion of subjects with clinically significant abnormal ECG findings • Proportion of subjects with non-significant abnormal findings • Change from Baseline in ECG intervals: - PR - QT, QTc and QTcF - RR - QRS • Proportion of subjects with maximum absolute QTcF values by category at Week 4 ≤450, >450 to ≤480, >480 to ≤500, >500 msec • Proportion of subjects with maximum change from Baseline in QTcF values by category at each post-baseline assessment time-point ≤0, >0 to ≤30, >30 to ≤60, >60 msec • Clinically significant changes in ECG findings are recorded as adverse events
BIOMARKER AND PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS	
ASSESSMENTS	ENDPOINTS
Plasma/serum for biomarkers collected: • At Baseline, End of Wash-out and Week 4 of each treatment period.	• Mean change from Baseline in the concentration of plasma/serum markers of inflammation and fibrosis
Plasma concentrations of orvepitant measured in spot samples: • At End of Washout and Week 4 of each treatment period.	• PK exposure-response relationship for the orvepitant group will be carried out on an exploratory basis to examine the possible relationship between clinical efficacy and plasma levels of the drug

SUBJECT POPULATION	
Inclusion Criteria Subjects must meet all the inclusion criteria to be eligible for the study	1. Male and female subjects ≥40 years of age 2. Able to understand and comply with the requirements of the study and give informed consent 3. Diagnosis of IPF established according to the 2018 or 2022 joint ATS/ERS/JRS/ALAT Clinical Practice Guideline 4. FEV1/FVC ratio ≥0.65 at the screening visit 5. Haemoglobin-corrected diffusion capacity of carbon monoxide (Hb-corrected DLCO) ≥25% within 12 months of the screening visit[1] 6. Arterial oxygen saturation on room air or oxygen ≥90% at Screening 7. Life expectancy of at least 12 months 8. Cough that is attributed to IPF, which has not responded to anti-tussive treatment, and which has been present for at least 8 weeks prior to Screening 9. Mean daily IPF Coughing Severity Scale score ≥5 (after rounding) during the second week of the baseline assessment period (assessed at Visit 2) 10. If taking pirfenidone or nintedanib[2], it must have been started at least 3 months prior to screening and the prescribed dose must have been stable for at least 1 month prior to Screening 11. Female subjects must not be of child-bearing potential (i.e., they must be surgically sterilised or post-menopausal[3]) 12. Male subjects who have partners of child-bearing potential must agree to use a condom from the Baseline visit until 30 days after the last dose of study medication
Exclusion Criteria Patients will not be permitted to participate in the study if they meet any of the exclusion criteria	1. Recent respiratory tract infection (<8 weeks prior to Screening) 2. Recent acute exacerbation of IPF (<8 weeks prior to Screening) 3. Current smokers or ex-smokers with <6 months' abstinence prior to Screening 4. Emphysema ≥50% on high-resolution computed tomography, or the extent of emphysema is greater

[1] Subjects who are unable to complete the DLCO assessment for reasons such as coughing may have this criterion waived

[2] Use of both nintedanib and pirfenidone is not permitted

[3] Post-menopausal is defined as >1 year since the last menstrual period for women >55 years of age or >1 year since their last menstrual period and have an FSH level in the menopausal range for women <55years of age.

	than the extent of fibrosis according to the reported results of the most recent scan 5. Mean early morning cough scale score ≥5 and rest of the day cough scale score <5 (after rounding) during the second week of the baseline assessment period (assessed at Visit 2) 6. Cough that is predominantly productive in nature and attributable to lung pathology such as chronic bronchitis or bronchiectasis 7. Known clinically significant pulmonary hypertension (World Health Organisation functional class III or IV) that is causing greater functional limitation than is attributable to IPF. 8. A history of clinically relevant drug or alcohol abuse [according to Diagnostic and Statistical Manual of Mental Disorders 5 criteria (or later edition if applicable)] within 6 months before Screening 9. Any other clinically significant or unstable medical or psychiatric condition that would, in the opinion of the investigator, interfere with the subject's ability to participate safely in the study 10. Any malignancy in the past 3 years unless non-invasive and in remission. Written approval must be obtained from the Sponsor for a subject with any history of malignancy 11. Any clinically significant abnormal laboratory test result(s), measured at Screening[4] 12. Inability to comply with the use of prohibited and allowed medications as described below: a. Strong or moderate inhibitors of CYP3A4 are not allowed from the day of Visit 2 until 1 week after the last dose of study medication b. Strong or moderate inducers of CYP3A4 are not allowed from Screening until 1 week after the last dose of study medication c. Strong or moderate P-glycoprotein inhibitors are not allowed from Screening until 1 week after the last dose of study medication d. Angiotensin converting enzyme (ACE) inhibitors are not allowed within 3 months of Screening and throughout the study

[4] The investigator should judge the clinical relevance of any abnormal laboratory parameters in the context of the subject's current and past medical history and any know contributing factors

	e. Other treatments for cough management (opioids, dextromethorphan, gabapentin, pregabalin, baclofen, antihistamines, thalidomide, benzonatate or tricyclic antidepressants (e.g. amitriptyline)) are not allowed from 4 weeks before the Baseline visit until Visit 8. Medications in these classes may be continued provided they have been prescribed solely for the management of another comorbidity and the dose has been stable for at least 4 weeks before the screening visit. f. The use of other NK_1 antagonists (eg aprepitant, fosaprepitant, rolapitant) is not permitted for any reason from 4 weeks before the Baseline visit until completion of Visit 8 g. Immune-suppressant drugs and systemic corticosteroids taken for co-morbidities are permitted provided the dose has been stable for at least 2 weeks before the screening visit and they are expected to be used at this dose throughout the study. Any other use is prohibited h. Supplemental oxygen is permitted provided it has been used for at least 2 weeks before the screening visit and is expected to be used throughout the study 13. Participation in any clinical research study evaluating another investigational drug or therapy within 30 days or within 5 half-lives (whichever is longer) of the investigational drug prior to Screening. If the subject was in an observational clinical study, no washout is required 14. Subjects who have previously received orvepitant at any time 15. Known allergy to any of the excipients used in the investigational medicinal product (IMP) (orvepitant or placebo tablets) 16. Subjects who, in the opinion of the Investigator, should not participate in the study for any other reason 17. Subjects who are dependent on the Sponsor, CRO or investigator for employment of education
PATIENT REPORTED OUTCOMES DEVELOPMENT AND VALIDATION After completing Visit 7, a subgroup of patients from sites in all participating countries will be invited to take part in detailed cognitive debriefing interviews. These interviews form part of the	

ongoing development and validation of the patient reported outcomes being used to assess burden of cough.	
STATISTICAL CONSIDERATIONS	
PLANNED SAMPLE SIZE	Assuming a common standard deviation of 2.7 for the difference between treatment periods, a sample size of 37 subjects per cohort (18-19 per sequence) has 90% power if the difference between treatments on the IPF Coughing Severity Scale is 1.5 points and assuming a two-sided type I error of 0.05, not adjusted for multiple comparisons. To allow for non-evaluable subjects/ missing data, the withdrawal rate and extent of missing data will be monitored as the trial progresses and the actual sample size will be increased accordingly such that data is available for 37 evaluable subjects.. Additional subjects (up to a maximum of 10 per cohort) may be recruited if the emerging IPF Coughing Severity Scale data is found to have greater variance than allowed for in the original sample size estimate. Subjects will be randomised to cohort and then further randomised to treatment order.
KEY ELEMENTS OF THE ESTIMAND	**Estimand:** Improvement in cough severity after 4 weeks of treatment, as assessed by change from baseline in IPF Coughing Severity Scale score. **Estimator:** Change from baseline in weekly mean IPF Coughing Severity Scale score **Intercurrent Event Strategies:** **S**ensitivity analyses will be undertaken to assess the impact of possible intercurrent events on the primary estimand. Intercurrent events that are expected to occur during the study are initiation of concomitant medication, withdrawal from study treatment, withdrawals from the study due to death.
STATISTICAL METHODS	Relevant Screening and Baseline data (i.e., data collected prior to the treatment administration), and demographic characteristics will be summarised descriptively for each treatment group. Efficacy and safety endpoints will be summarised by descriptive statistics for each treatment group and for each time point. All statistical hypothesis tests and confidence intervals will be two sided, using a type I error rate of 0.05. No adjustments for multiple comparisons are planned for this study. The primary analysis of change from baseline in weekly average of the mean daily IPF Coughing Severity Scale

	score will be conducted via an ANCOVA model. Secondary efficacy endpoints will also be analysed using an ANCOVA model. The safety and tolerability profile will be assessed versus Baseline conditions and differences between treatment groups and descriptive statistics will be produced, where applicable. Plasma concentrations of orvepitant will be summarised descriptively; possible exposure-response relationships will be explored. Selected efficacy parameters will be summarised and analysed for the following sub-groups: - By use of concomitant disease modifying therapies at Baseline (yes, no [nintedanib and/or pirfenidone]) - By IPF Coughing Severity Scale score at Baseline - By cough frequency at Baseline Other sub-groups (e.g., age, sex, ethnicity) will be evaluated if there are sufficient subjects to warrant analysis. Selected safety parameters will be summarised for the following sub-groups: - By use of concomitant disease modifying therapies at Baseline (yes, no [nintedanib or pirfenidone])
STUDY MEDICATION	
ORVEPITANT FORMULATION/DOSE	Orvepitant 10 mg tablets Orvepitant 30 mg tablets
REFERENCE FORMULATION/DOSE	Matching placebo
ROUTE OF ADMINISTRATION	Oral
DURATION/FREQUENCY OF TREATMENT	Once daily dosing in the evening for 28 days in each of the two Treatment Periods

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

ACM	Ambulatory Cough Monitor
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of covariance
BP	Blood Pressure
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
DLCO	Diffusion Capacity for Carbon Monoxide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EGFRi	Epidermal Growth Factor Receptor inhibitor
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GRC	Global Rating of Change
GRS	Global Rating of Status
H0	Null Hypothesis
H1	Alternative Hypothesis
HADS	Hospital Anxiety and Depression Scale
HARQ	Hull Airway Reflux Questionnaire
IB	Investigators Brochure
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IPF	Idiopathic Pulmonary Fibrosis
IWRS	Interactive Web Response System
K-BILD	Kings Brief Interstitial Lung Disease (questionnaire)
LCQ	Leicester Cough Questionnaire
MeDRA	Medical Dictionary for Regulatory Activities
NK	Neurokinin
NRS	Numerical Rating Scale
PAH	Pulmonary Arterial Hypertension

PK	Pharmacokinetic
Pop PK	Population PK
PRO	Patient Reported Outcome
PROMIS SD SF 8b	Patient-Reported Outcomes Measurement Information System Sleep Disturbance short form 8b questionnaire
RUCC	Refractory or Unexplained Chronic Cough
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SP	Substance P
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TMF	Trial Master File
VAS	Visual Analogue Scale

4. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Chief Investigator

[redacted]

Sponsor's Medical Expert

[redacted]
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Contract Research Organization / Monitors

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Statistical Consultants

[redacted]

GENERAL INFORMATION (continued)

Central Clinical Laboratories	[redacted]
Pharmacokinetic Laboratory	[redacted]
Biomarker Laboratory	[redacted]
Ambulatory Cough Monitor Provision and Reading Centre	King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK
Pharmacovigilance Provider	[redacted]

5. BACKGROUND INFORMATION

5.1 Orvepitant

Orvepitant is a potent and selective inhibitor of the human neurokinin (NK) 1 receptor where it blocks the effects of Substance P (SP), the preferred endogenous ligand of the NK_1 receptor. The safety and efficacy of orvepitant has previously been evaluated in more than 900 patients and healthy volunteers, including two studies in patients with chronic cough. A full summary of the pharmacology, pre-clinical safety, pharmacokinetics and clinical safety and efficacy can be found in the current version of the Orvepitant Investigator's Brochure.

5.2 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a rare and specific form of chronic, progressive, fibrosing interstitial pneumonia in which fibrosis is limited to the lungs. The prevalence is difficult to determine accurately because of the diagnostic criteria used and the populations examined, but the best estimates put the prevalence in the United States (US) at between approximately 14 per 100,000 using narrow criteria and 43 per 100,000 using broad criteria [1]. The National Institute for Health and Care Excellence estimates that the prevalence in the United Kingdom is around 15 to 25 per 100,000 population [2]. The histologic appearance on biopsy is of usual interstitial pneumonia (UIP). IPF is a diagnosis of exclusion and other causes of lung fibrosis, particularly connective tissue disorders, need to be considered and excluded. Diagnosis is made on the basis of high-resolution computerised tomography scan findings and histopathology, where available. The etiology is unknown [3].

The incidence of IPF increases with older age, with presentation typically consisting of insidious onset of symptoms in the sixth and seventh decades of life [1]. It is more common in men than women and most patients are current or past smokers [4]. A history of gastro-oesophageal reflux is also common [5,6]. IPF usually assumes a course of relentless physiologic deterioration although in some patients it remains stable for extended periods. Nonetheless, the prognosis is worse than that of many cancers and other forms of lung fibrosis, and median life expectancy after diagnosis is just 2 to 5 years [7].

The symptoms of IPF have typically been present for months to years before diagnosis. Breathlessness with exertion and cough are the most common symptoms that lead to diagnosis. Fatigue and anxiety are also common symptoms. Bi-basilar fine inspiratory crackles (so-called Velcro crackles) are the most frequent physical examination finding and digital clubbing is seen in 25 to 50% of patients. Features of right heart failure and peripheral oedema develop late in the clinical course [4,8].

A minority of patients is eligible for lung transplantation and so, in the absence of a 'curative' treatment, the goal of therapy is to slow disease progression and two antifibrotic drugs which achieve this are available (pirfenidone and nintedanib). It is doubtful whether antifibrotic drugs are able to improve dyspnea and cough. Given the limited improvements that can be made to the underlying disease, alleviating symptoms and improving quality of life is both a goal and a major challenge of treatment [9].

5.3 Cough in Patients with IPF

Cough is a common symptom in patients with IPF and is one of the most burdensome aspects of the disease [10]. However, the overall prevalence of cough is unclear, probably due to differences in the definitions used to determine cough (any versus disabling cough). In some studies, up to 80% of patients report cough [4,11] although lower prevalence has also been reported [12].

When cough is present it is often severe and difficult to treat [13]. The cough of IPF is chronic and is most often described as dry and non-productive, although a productive cough can occur, particularly on waking from sleep. It is often accompanied by a sense of continually having the urge to cough that is not relieved by coughing [14].

The burden of cough in IPF is high. The limited data available on frequency shows average awake cough counts of up to 55 coughs/hour [13,15] with a range that can occur into the hundreds. This frequency is higher than most respiratory disorders associated with chronic cough but not as high as RUCC [13]. In treatment studies (in which patients are selected because they have significant cough symptoms) the average cough severity scores at baseline are typically greater than 65 mm on a 100 mm VAS [13,15]. This burden is similar to that of patients with refractory chronic cough presenting to specialist cough clinics and is greater than that of cough in asthma or chronic obstructive pulmonary disease [13].

Chronic cough, regardless of its cause, can impact markedly on health-related quality of life [16,17]. Co-morbid sequelae of repeated coughing can include musculoskeletal chest pain, fatigue, sleep disturbance, urinary incontinence and, in extreme cases, syncope or rib fractures. Chronic cough can cause relationship difficulties, avoidance of public areas (particularly during the current COVID-19 situation), decreased social interaction and work-related problems affecting physical, mental and social health [18].

5.4 Cough Hypersensitivity in IPF

Most respiratory diseases associated with cough, such as chronic bronchitis, asthma and acute viral infections, predominantly affect the airways or upper respiratory tract where sensory innervation is dense. By contrast, pathological changes in IPF principally affect the lung parenchyma and alveoli where innervation is sparse. It is therefore surprising that cough is so common in this disorder [19]. The pathophysiology of cough in IPF is not yet fully understood, but whilst it is most likely multi-factorial in origin, at least in part it is due to development of hypersensitivity in the cough reflex pathway [9]. Possible explanations for the hypersensitivity are that mechanical distortion of the lung, caused by the fibrosis, directly influences afferent nerve fibres, and/or that efferent nerves that inhibit cough are destroyed by the fibrosis [9]. An imbalance between afferent stimuli and the (efferent) responses then results in increased coughing such that minor, and usually innocuous, stimuli such as talking, eating, temperature change and aromas triggers a cough.

Capsaicin, when inhaled, induces coughing and the dose of capsaicin required to trigger coughing is an indicator of the sensitivity of the cough reflex pathway. Evidence that IPF patients have an increased cough reflex sensitivity is provided by studies showing an amplified response to inhaled capsaicin compared to healthy controls [20,21]. Hypersensitivity of the cough reflex pathway has also been shown by the increased cough reflex sensitivity response induced by mechanical percussion of the chest wall in IPF patients [19]. The sensitivity is greatest over the lung base where fibrosis is most extensive. These data not only demonstrate hypersensitivity of the cough reflex but support the hypothesis that lung distortion contributes to the pathogenesis of cough in IPF.

5.5 Role of Substance P and the NK_1 Receptor System in Cough Hypersensitivity

The airways are innervated by vagal sensory nerve fibres, some of which evoke coughing when activated [22]. Patients with chronic cough hypersensitivity likely have elevated levels of proinflammatory mediators. Vagal sensory nerve terminals within the airway mucosa express a range of receptors for these proinflammatory mediators and continued activation results in altered sensory neuron activity. Blocking sensory nerve activation by inflammatory mediators (notably with P2X3 receptor antagonists) has proved promising but does not completely suppress excessive coughing, suggesting multiple mechanisms may need to be targeted [23].

Vagal sensory neurons synapse in the brainstem cough centre and connect into circuits that ascend to the higher brain. Reflex cough, the urge to cough and behavioural modulation of coughing can occur through these lower and higher order brain circuits. Evidence supports an imbalance of ascending excitatory activity and reduced descending inhibitory activity in brain networks controlling cough in patients with cough hypersensitivity [22].

Among the neuromodulators that are up-regulated in cough hypersensitivity is SP. It does not appear to be functionally important under normal physiological conditions [24] but is implicated in induction and maintenance of peripheral and central cough reflex hypersensitivity [24-26]. SP has been identified as one of the neurotransmitters released by vagal afferent c-fibres in the brainstem cough centre which activate post synaptic brainstem neurons and hence propagate the signal to cough [27].

In addition to the central role, a direct role in stimulating cough in IPF has been shown for SP [21]. Hope-Gill and colleagues found that inhaled SP induced a cough response within a few seconds in seven of ten IPF patients compared with none of the ten healthy volunteers.

Raised levels of SP in biological fluids (plasma, induced sputum, nasal secretions and bronchoalveolar lavage fluid) have been reported in patients suffering with multiple different cough conditions [27-31], including cough associated with asthma and acid reflux, post-infectious cough and RUCC.

As previously noted, patients with IPF [21], as well as those with acute cough [32], also appear to have increased sensitivity to SP cough challenge. In animal models, cough can be induced by direct injection of SP into the brainstem [33] and evoked cough (induced by, for example, capsaicin inhalation) can be blocked with NK1 receptor antagonists[25].

5.6 Orvepitant in the Treatment of Cough Hypersensitivity

A cough hypersensitivity syndrome can occur both in patients with and without underlying pulmonary disease [34,35]. In many patients with a chronic cough (defined as a cough of at least 8 weeks' duration) there is either no obvious underlying cause for the cough or it is refractory to treatment of the underlying disease (refractory or unexplained chronic cough, RUCC). It is now well established that patients with RUCC have increased sensitivity of the cough reflex pathway such that they cough in response to what should be an innocuous stimulus, for example singing, talking, perfumes and cold air at all (allotussia) and have increased sensitivity to noxious stimuli (hypertussia) [36]. This has been demonstrated experimentally in many challenge studies with, for example, inhaled capsaicin [37-40].

The frequency of coughing in this group of patients tends to be higher than in other disorders associated with chronic cough [13,40]. RUCC patients commonly report a sensation of an urge to cough which is not relieved by coughing [41] and have a reduced ability to voluntarily inhibit coughing [37]. Collectively, these characteristics indicate a form of sensory neuropathy.

Orvepitant has been evaluated in two Phase 2 studies in patients with RUCC and has shown clear evidence of benefit in these trials. The first study, VOLCANO-1, was an open label pilot study in 13 subjects. After 4 weeks of treatment with orvepitant 30 mg once daily there was a significant reduction from baseline in awake cough frequency (-18.9 coughs/hour, $p<0.001$) that appeared to be sustained for a further 4 weeks after the end of treatment. After 4 weeks there were also improvements in the cough severity VAS (approximately 28% reduction from baseline, $p=0.002$) and a small (~8%) but significant improvement in the Cough Quality of Life Questionnaire score.

The second study, VOLCANO-2, was a randomised, double-blind, placebo-controlled dose range finding study. Three hundred and fifteen RUCC patients were randomised to receive placebo or orvepitant 10, 20 or 30 mg once daily for 12 weeks. Orvepitant improved all the patient reported

outcomes (PRO) assessed in the study, with the improvements being most evident with the 30 mg dose of orvepitant. These are summarised for each dose at Week 12 in Table 1.

Table 1. Summary of patient reported measures of cough burden after 12 weeks treatment in patients with refractory or unexplained chronic cough

Percentage change from baseline^	Placebo	Orvepitant		
		10 mg	20 mg	30 mg
N (full analysis set)	76	73	77	76
Cough severity VAS (day)	-15.8	-27.1	-17.5	-29.5*
Cough severity VAS (night)	-3.3	-22.5*	-15.9	-21.7*
Urge to cough VAS	-16.9	-32.5*	-18.3	-32.7*
Leicester Cough Questionnaire	13.6	23.1	19.3	-31.7*

^ Percentage change estimates are based on group mean values and are presented here to enable comparison across endpoints to be made

* $p<0.05$ compared to placebo based on a mixed model for repeated measures including region, baseline value, treatment, week, week by region interaction, week by baseline interaction and week by treatment interaction as explanatory variables, and subject as a random effect

It was a feature of the study results that in almost every analysis the response was greatest with the 30 mg dose, but the response was not always dose-ordered for the lower two doses. The reasons for this are not clear although it may reflect that neither the 10 mg nor the 20 mg doses will result in full central NK_1 receptor occupancy and hence the response to both these doses is sub-optimal.

Reductions from baseline in awake cough frequency (the primary efficacy endpoint in the study) were observed in all treatment groups, including placebo, at all timepoints in the full analysis set. Although there was a greater reduction in the orvepitant 30 mg group at Week 12 (geometric mean ratio vs baseline 0.54) the substantial placebo response at this timepoint prevented any meaningful treatment effect from being discerned.

In a pre-defined analysis, subjects were divided into higher and lower cough frequency sub-groups according to whether their baseline awake cough frequency was above or below the overall study population median (32 coughs/hour). In the higher frequency cough group (>32 coughs/hour) there was a more orderly placebo response and the separation from placebo for the orvepitant 30 mg dose was, as a result, much more apparent at all time points. The difference between orvepitant 30 mg and placebo at Week-12 only just failed to achieve significance ($p=0.066$) despite the study not having been powered for analysis of the sub-groups. The 10 mg and 20 mg dose groups showed improvements compared to placebo initially, but these improvements were not sustained beyond Week 2.

In marked contrast, the changes from baseline in the lower frequency cough group (baseline awake cough frequency <32) were less orderly, and in particular showed the exaggerated (compared to earlier time-points) placebo reduction at Week 12 which confounded the ability to interpret the primary endpoint in the full analysis set.

It is possible that the apparent disconnect between the PROs and cough frequency assessment is a true reflection of the actual profile of effect of orvepitant on different aspects of the overall cough burden. However, several recent interventional studies with potential new chronic cough therapies have also found that a benefit on cough frequency cannot be shown when the baseline cough

frequency is low. Most notably, in the pooled analysis of the two phase 3 studies with the P2X3 antagonist gefapixant in more than 2000 patients with RUCC there is no effect of treatment on cough frequency in the lower frequency sub-group whereas there is a significant improvement in the higher frequency sub-group [42,43].

6. STUDY OBJECTIVES AND PURPOSE

6.1 Primary objectives

- To evaluate the effect of orvepitant once daily on cough severity, as perceived by patients, with IPF
- To evaluate the safety of orvepitant once daily in patients with IPF

6.2 Secondary objectives

- To evaluate the effect of orvepitant once daily on other measures of cough burden and on health-related quality of life in patients with IPF
- To evaluate the effect of orvepitant on other comorbidities in patients with IPF

6.3 Exploratory objectives

- To evaluate the effect of orvepitant once daily on markers of disease activity in patients with IPF
- To evaluate the relationship between plasma concentrations of orvepitant and efficacy in patients with IPF

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Subject numbers

In the first instance, approximately 88 subjects will be recruited into the study in two equal sized cohorts.

The number of subjects enrolled may be increased to a maximum of 108 if the interim sample size re-estimation indicates that 88 is insufficient (see Section 11.3).

Subjects will be enrolled at approximately 30 sites across North America and Europe. Additional sites and regions may be added.

7.2 Inclusion criteria

1. Male and female subjects ≥40 years of age
2. Able to understand and comply with the requirements of the study and give informed consent
3. Diagnosis of IPF established according to the 2018 or 2022 joint ATS/ERS/JRS/ALAT Clinical Practice Guideline
4. FEV1/FVC ratio ≥0.65 at the screening visit
5. Haemoglobin-corrected diffusion capacity of carbon monoxide ≥25% within 12 months of the screening visit[5]
6. Arterial oxygen saturation on room air or oxygen ≥90% at Screening
7. Life expectancy of at least 12 months
8. Cough that is attributed to IPF, which has not responded to anti-tussive treatment, and which has been present for at least 8 weeks prior to Screening
9. Mean daily IPF Coughing Severity Scale score ≥5 (after rounding) during the second week of the baseline assessment period (assessed at Visit 2)
10. If taking pirfenidone or nintedanib[6], it must have been started at least 3 months prior to screening and the prescribed dose must have been stable for at least 1 month prior to screening
11. Female subjects must not be of child-bearing potential (i.e., they must be surgically sterilised or post-menopausal[7])
12. Male subjects who have partners of child-bearing potential must agree to use a condom from the Baseline visit until 30 days after the last dose of study medication

7.3 Exclusion criteria

A subject meeting any of the following exclusion criteria will not be permitted to participate:

1. Recent respiratory tract infection (<8 weeks prior to Screening)
2. Recent acute exacerbation of IPF (<8 weeks prior to Screening)
3. Current smokers or ex-smokers with <6 months' abstinence prior to Screening

[5] Subjects who are unable to complete the DLCO assessment for reasons such as coughing may have this criterion waived

[6] Use of both nintedanib and pirfenidone is not permitted

[7] Post-menopausal is defined as >1 year since the last menstrual period for women >55 years of age or >1 year since their last menstrual period and have an FSH level in the menopausal range for women <55years of age.

4. Emphysema ≥50% on high-resolution computed tomography, or the extent of emphysema is greater than the extent of fibrosis according to the reported results of the most recent scan
5. Mean early morning cough scale score ≥5 and rest of the day cough scale score <5 (after rounding) during the second week of the baseline assessment period (assessed at Visit 2)
6. Cough that is predominantly productive in nature and attributable to lung pathology such as chronic bronchitis or bronchiectasis
7. Known clinically significant pulmonary hypertension (World Health Organisation functional class III or IV) that is causing greater functional limitation than is attributable to IPF.
8. A history of clinically relevant drug or alcohol abuse [according to Diagnostic and Statistical Manual of Mental Disorders 5 criteria (or later edition if applicable)] within 6 months before Screening
9. Any other clinically significant or unstable medical or psychiatric condition that would, in the opinion of the investigator, interfere with the subject's ability to participate safely in the study
10. Any malignancy in the past 3 years unless non-invasive and in remission. Written approval must be obtained from the Sponsor for a subject with any history of malignancy
11. Any clinically significant abnormal laboratory test result(s), measured at Screening[8]
12. Inability to comply with the use of prohibited and allowed medications as described below:
    a. Strong or moderate inhibitors of CYP3A4 are not allowed from the day of Visit 2 until 1 week after the last dose of study medication
    b. Strong or moderate inducers of CYP3A4 are not allowed from Screening until 1 week after the last dose of study medication
    c. Strong or moderate P-glycoprotein inhibitors are not allowed from Screening until 1 week after the last dose of study medication
    d. Angiotensin converting enzyme (ACE) inhibitors are not allowed within 3 months of Screening and throughout the study.
    e. Other treatments for cough management (opioids, dextromethorphan, gabapentin, pregabalin, baclofen, antihistamines, thalidomide, benzonatate or tricyclic antidepressants (e.g. amitriptyline)) are not allowed from 4 weeks before the Baseline visit until Visit 8. Medications in these classes may be continued provided they have been prescribed solely for the management of another comorbidity and the dose has been stable for at least 4 weeks before the screening visit.
    f. The use of other NK_1 antagonists (e.g., aprepitant, fosaprepitant, rolapitant) is not permitted for any reason from 4 weeks before the Baseline visit until completion of Visit 8
    g. Immune-suppressant drugs and systemic corticosteroids taken for co-morbidities are permitted provided the dose has been stable for at least 2 weeks before the screening visit and they are expected to be used at this dose throughout the study. Any other use is prohibited.
    h. Supplemental oxygen is permitted provided it has been used for at least 2 weeks before the screening visit and is expected to be used throughout the study.

[8] The investigator should judge the clinical relevance of any abnormal laboratory parameters in the context of the subject's current and past medical history, and any know contributing factors

13. Participation in any clinical research study evaluating another investigational drug or therapy within 30 days or within 5 half-lives (whichever is longer) of the investigational drug prior to Screening. If the subject was in an observational clinical study, no washout is required
14. Subjects who have previously received orvepitant at any time
15. Known allergy to any of the excipients used in the investigational medicinal product (IMP) (orvepitant or placebo tablets)
16. Subjects who, in the opinion of the Investigator, should not participate in the study for any other reason.
17. Subjects who are dependent on the Sponsor, CRO or investigator for employment of education.

7.4 Withdrawal criteria

The subjects will be informed that they have the right to withdraw from the study at any time without stating a reason and without prejudice to further treatment.

The Investigator may withdraw subjects from the study or may discontinue study treatment at any time.

Withdrawal from the study or early discontinuation from the IMP is to be registered in the electronic Case Report Form (eCRF).

Early withdrawal or early discontinuation from the IMP of any subject who has given informed consent to participate will be recorded including the reason for withdrawal. The primary reason will be selected from the following standard categories of early discontinuations or withdrawals:

- Failed to meet randomisation criteria (**screen failure**)
- **Adverse Event**: One or more adverse events (AE) occurred that in the medical judgment of the investigator are grounds for discontinuation from participation in the best interests of the subject
- **Withdrawal of Consent**: The subject desired to withdraw from further participation in the study. The subject is not obliged to provide any reason for withdrawal of consent, but where a reason is given, this will be recorded on the electronic Case Report Form (eCRF)
- **Protocol Violation**: The subject failed to adhere to the protocol requirements, and in the opinion of the investigator, this failure to comply increased the risk to the subject to an unacceptable level.
- **Lost to Follow-Up**: The subject stopped coming for visits and study personnel were unable to contact the subject.
- **Other:** The subject was terminated for a reason other than those listed above

Subjects who withdraw or are withdrawn from participation in the study after randomisation should attend an Early Termination visit at which the procedures scheduled for the Visit 8 Follow Up will be undertaken. If the subject withdraws due to an AE, the event should be followed until resolution or care is transferred to the subject's usual physician.

Subjects who are withdrawn after randomisation will not be replaced.

In some circumstances, the Investigator may discontinue study treatment without the need to withdraw the subject from participation in the study. When subjects permanently discontinue IMP, effort should be made to continue following the subject through to the end of scheduled visits for safety and to obtain efficacy assessments that can be assigned to the originally randomised treatment.

7.5 Criteria for Stopping the Study

The Sponsor may terminate the study for safety or administrative reasons at any time.

The safety of orvepitant will be monitored by the Data Safety Monitoring Board (DSMB). Full details of the DSMB's role and the specific criteria for stopping the study for safety reasons are described in the ORV-PF-01 DSMB Charter.

8. STUDY DESIGN

8.1 Primary endpoint

The primary endpoint is the mean change from Baseline to Week 4 (the last 7 days of treatment) in weekly average of the daily IPF Coughing Severity Scale score.

8.2 Secondary efficacy endpoints

The secondary efficacy endpoints comprise:

Assessments	Secondary Efficacy Endpoints
IPF Coughing Severity Scale	• Mean change from Baseline to Week 2 in weekly average of the daily IPF Coughing Severity Scale
Early morning cough scale	• Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily early morning cough scale
Rest of the day cough scale	• Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily rest of the day cough scale
Urge to cough scale	• Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily urge to cough scale
Cough frequency scale	• Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily cough frequency scale
Dyspnoea scale	• Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily dyspnoea scale
Patient global ratings of status for all coughing, early morning coughing and rest of the day coughing	• Proportion of subjects in each category at Weeks 2 and 4
Patient global ratings of change for all coughing, early morning coughing and rest of the day coughing	• Proportion of subjects in each category at Weeks 2 and 4
Cough frequency measured using the Leicester Cough Monitor ambulatory cough monitor	• Mean change from Baseline to Week 4 in 24-hour cough frequency • Mean change from Baseline to Week 4 in awake cough frequency • Mean change from Baseline to Week 4 in night-time cough frequency • Mean change from Baseline to Week 4 in the number of coughing bouts
Leicester Cough Questionnaire (LCQ)	• Mean change from Baseline to Week 4 in LCQ total and domain (Physical, Social, Psychological) scores
King's Brief Interstitial Lung Disease health status questionnaire (K-BILD)	• Mean change from Baseline to Week 4 in K-BILD total and domain (Psychological, Breathlessness and Chest Symptoms) scores

	• Proportion of patients with a clinically relevant improvement in total K-BILD score
PROMIS SF SD 8b sleep assessment questionnaire	• Mean change from Baseline to Week 4 in the PROMIS SF SD 8b score
Hospital Anxiety and Depression Scale (HADS) questionnaire	• Mean change from Baseline to Week 4 in the HADS score
Hull Airway Reflux Questionnaire (HARQ)	• Mean change from Baseline to Week 4 in HARQ score

8.3 Safety endpoints

The safety endpoints comprise the following:

Assessments	**Safety endpoints**
Pulmonary function tests measured using a spirometer	• Change from Baseline to each post-baseline assessment time-point in forced vital capacity (FVC), forced expired volume in one second (FEV1), peak expiratory flow rate and vital capacity (VC)
Adverse events recorded throughout the study	• Number of treatment emergent adverse events • Number of treatment emergent serious adverse events • Number of treatment emergent adverse events resulting in treatment discontinuation • Severity of treatment emergent adverse events • Number of treatment emergent related adverse events
Physical Examination	• Treatment emergent changes in physical examination will be recorded as adverse events
Vital Signs (pulse rate, systolic and diastolic blood pressure, arterial oxygen saturation, temperature, weight).	• Mean change from Baseline to each post-baseline assessment time-point in each vital sign: - Systolic blood pressure - Diastolic blood pressure - Pulse rate - Temperature - Arterial oxygen saturation - Weight • Clinically significant changes in vital signs are recorded as adverse events

Haematology, clinical chemistry and urinalysis parameters	• Mean change from Baseline to each post-baseline assessment time-point in each haematology parameter • Mean change from Baseline to each post-baseline assessment time-point in each clinical chemistry parameter • Shift from Baseline to each post-baseline assessment time-point in each urinalysis parameter • Clinically significant changes in laboratory parameters are recorded as adverse events
12-lead ECG parameters	• Proportion of subjects with clinically significant abnormal ECG findings at each post-baseline assessment time-point • Proportion of subjects with non-significant abnormal findings at each post-baseline assessment time-point • Change from Baseline to each post-baseline assessment time-point in ECG intervals: - PR - QT, QTc and QTcF - RR - QRS • Proportion of subjects at each post-baseline assessment time-point with maximum absolute QTcF values by category - $\leq$450, >450 to $\leq$480, >480 to $\leq$500, >500 msec • Proportion of subjects at each post-baseline assessment time-point with maximum change from baseline in QTcF values by category - $\leq$0, >0 to $\leq$30, >30 to $\leq$60, >60 msec • Clinically significant changes in ECG findings are recorded as adverse events

8.4 Exploratory endpoints

The following exploratory endpoints will be assessed:

Assessments	Exploratory Endpoints
Plasma/serum biomarkers	• Mean change from Baseline in the concentration of plasma/serum markers of inflammation and fibrosis
Plasma concentrations of orvepitant measured in spot samples	• PK exposure-response relationship for the orvepitant group will be carried out to examine the possible relationship between clinical efficacy and plasma levels of the drug

8.5 Patient Reported Outcomes Development and Validation

A sub-set of patients participating in the study will be invited to participate in detailed cognitive debriefing interviews. These interviews form part of the ongoing development and validation of the patient reported outcomes measures being used to assess burden of cough, and in particular the IPF Coughing Severity Scale.

The interviews will be scheduled to take place soon after patients have completed Visit 7 so that their memory of the assessments and the burden of cough, they experienced at the time is still relatively fresh. A similar number of patients from each country participating in the study will be interviewed. A minimum of 16 subjects will be interviewed with additional subjects interviewed until saturation of responses for each of the key concepts being evaluated is reached.

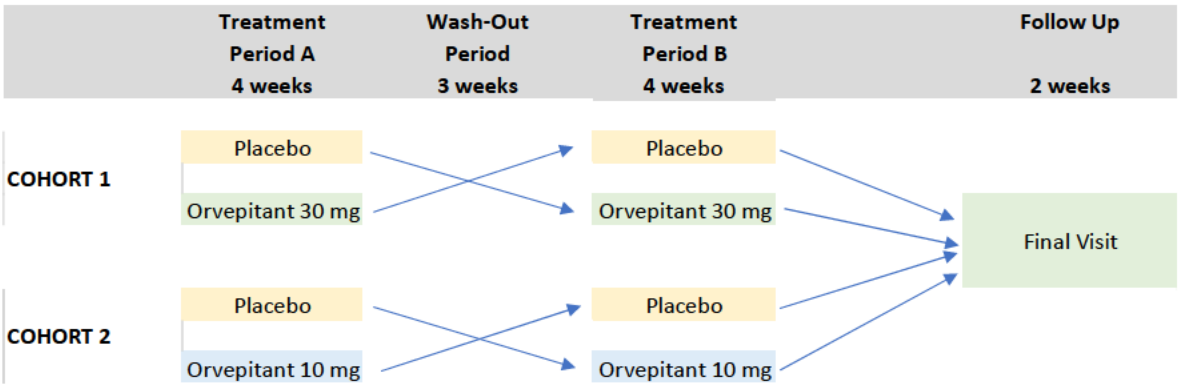
8.6 Study design

The study will have a multi-center, double-blind, randomised, placebo-controlled 2-period cross-over design. Two doses of orvepitant, 10 and 30 mg once daily, will be evaluated.

Subjects will participate in one of two cohorts (Cohort 1 [30 mg] and Cohort 2 [10 mg]). Within each cohort, subjects will be randomised to receive either orvepitant or placebo in the first treatment period (Treatment Period A) followed by the alternate treatment in Treatment Period B. There will be a wash-out period of 3 weeks between the two treatment periods. Subjects will be randomised 1:1 to each of the two treatment orders and 1:1 to each cohort.

Subjects will enter a screening period of between 14 and 28 days to determine eligibility. Eligible subjects will be randomised at the Baseline visit and will participate in two identical 4-week treatment periods with the wash-out period between them. There will be a total of 8 visits including the Screening, Baseline, and final Follow-up visits (Table 2).

Figure 1. Study Schematic



8.6.1 Justification for Study Design

The study is designed to allow an initial assessment of both the efficacy and safety of orvepitant in patients with cough due to IPF.

Allocation bias is avoided by randomisation and assessment bias is avoided by use of a fully blinded placebo control treatment period. The study employs a cross-over design to enable an assessment of efficacy to be made using fewer subjects than would be required for a parallel group design. IPF is a rare disease and so suitable subjects are scarce, even in the specialist interstitial lung disease units where the study will be undertaken. The use of two separate cohorts of subjects enables two doses of orvepitant to be evaluated while keeping the number of blinded treatment periods to two. Use of two cohorts also increases the total number of subjects in whom safety experience is gained. A sample size estimate has been undertaken to determine the number of subjects required to demonstrate efficacy based on reasonable assumptions and currently available data (see Section 11.3). Should emerging data indicate that the assumptions used were incorrect, the protocol allows for an increase in the total number of subjects enrolled to ensure that the efficacy objectives of the study can still be met.

The treatment duration in each period is 4 weeks. In the two previous studies with orvepitant in chronic cough the treatment benefits that were observed were evident within 2 weeks after the start of treatment and in the 12-week VOLCANO-2 study the effect at 12 weeks was similar to that seen after 4 weeks. Studies with other investigational treatments for chronic cough have shown a similar pattern of response, enabling conclusions on the likely long-term efficacy to be drawn after this time.

A potential limitation of any cross-over study is the occurrence of confounding carry over effects between treatment periods. The wash-out period for this study is 3-weeks which, given that the half-life of orvepitant is approximately 33 hours, is expected to be sufficient for the drug to be fully cleared and for cough symptoms to return to baseline levels.

The safety of orvepitant as a treatment for chronic cough in patients with IPF will be assessed against a reference (placebo) treatment period such that the relative incidence of any emerging safety findings can be compared.

8.7 Study Visits

8.7.1 Screening

Subjects will provide informed consent before any screening procedures are undertaken. If the subject is taking a prohibited concomitant mediation which can be safely discontinued, then

informed consent must be taken first. The formal screening visit may then be delayed to allow completion of the concomitant medication wash-out period such that the screening assessments are completed within 28 days before the Baseline visit.

The screening period will last a minimum of 14 days so that the baseline electronic diary (eDiary) assessment can be completed.

The Screening visit will include the following assessments to determine the subject's eligibility for inclusion into the study:

- Full physical examination, 12 lead ECG, vital signs, pulse oximetry and spirometry (FEV_1 and FVC)
- If the subject has not had diffusion capacity of carbon monoxide (DLCO) measured within 12 months before screening, then this should be undertaken at the screening visit[9].
- Recording of the subject's medical history, and prior and concomitant medication use, in particular other concomitant respiratory medications, both prescribed and/or over the counter medications
- Blood sampling for clinical chemistry and haematology, and urine sample collection urinalysis

Subjects should be carefully pre-screened so that the outcome of most eligibility criteria can be anticipated at the formal screening visit. If necessary, non-routine assessments (e.g., DLCO) should be pre-arranged for the screening visit.

Subjects who satisfy all criteria (other than safety laboratory tests the results of which are unlikely to be immediately available) and in whom no clinically relevant laboratory abnormalities are anticipated can be provided with the eDiary and be trained on its use (including review of a patient information video). The eDiary should be completed for 14 days before the subject returns for the baseline visit.

8.7.2 Baseline Visit (Visit 2)

A limited set of data will be collected for subjects who withdraw from the study after providing informed consent but prior to randomisation onto the study (Screen Failures).

Eligibility for randomisation will be reviewed based on the results of the eDiary cough score recordings. To be eligible to continue the subject must:

- Have completed the eDiary on at least 4 of the 7 days prior to the Visit
- Meet the cough scale score eligibility criteria (Sections 7.1 and 7.2).

The subject's general health status should be reviewed to confirm that there have been no changes which might make them ineligible.

The Baseline visit will be Day 0. Prior to randomisation on Day 0, the following assessments will be completed:

- Symptom directed physical examination
- Vital signs (after resting for ≥ 5 mins)
- Spirometry

[9] Subjects who are unable to complete the DLCO assessment for reasons such as coughing may have this criterion waived

- 12-lead ECG
- Safety labs: blood samples for clinical chemistry and hematology and urine sample for urinalysis
- Blood sample for biomarkers
- Subjects will be asked to complete the study questionnaires: GRS, LCQ, K-BILD, PROMIS SD SF8b, HADS and HARQ
- Subjects will be fitted with an ambulatory cough monitor (ACM), which will be initiated prior to the subject leaving the clinic to monitor cough frequency over the next 24 hours. Immediately after the end of this period the subjects will either return the ACM to the clinic or collection of the ACM from the subjects will be organised.
- A review of changes in concomitant medications and any changes in health status (AEs)

The subjects will be reminded of the eDiary completion requirements and will undergo re-training on the use of the diary if required.

Eligible subjects will be randomised on Day 0 in a 1:1 ratio to either Cohort 1 or Cohort 2, and then within each cohort will be further randomised in a 1:1 ratio to receive either placebo or orvepitant in Treatment Period A. Randomisation will be performed centrally via an IWRS.

Subjects will be dispensed sufficient study medication for 28 days (plus overage) which they should begin taking the evening of the following day before retiring to bed. Starting study medication, the following day enables ACM monitoring to be completed before study medication starts.

8.7.3 Visits 3 and 6

Visits 3 and 6 should be scheduled 14 (±3) days after the start of each Treatment Period. The assessments are to be undertaken remotely by telephone or videoconference.

A review for adverse events or changes in concomitant medications will be undertaken.

Subjects will complete the GRS and GRC assessments (verbally) and will be reminded of the eDiary completion requirements, as necessary.

8.7.4 Visit 4

Visits 4 should be scheduled 28 (±3) days after the Baseline visit. The following assessments and procedures will be undertaken at the clinic site or during a home visit:

- Vital signs
- Spirometry
- 12-lead ECG
- Safety labs: blood samples for clinical chemistry and hematology and urine sample for urinalysis
- Blood sample for biomarkers
- Blood sample for orvepitant concentration
- Subjects will be asked to complete the study questionnaires: GRS and GRC, LCQ, K-BILD, PROMIS SD SF8b, HADS and HARQ
- Subjects will be fitted with an ambulatory cough monitor (ACM), which will be initiated prior to the subject leaving the clinic to monitor cough frequency over the next 24 hours.

Immediately after the end of this period the subjects will either return the ACM to the clinic or arrangements will be made to collect it from the subject.

- A review of changes in concomitant medications and any changes in health status (AEs)

The subjects will undergo re-training on the use of the diary, if required, and will be reminded of the need to continue to record their IPF Coughing Severity Scale, additional cough scales and other symptom scales in the eDiary during the wash-out period.

Study medication compliance for Treatment Period A will be checked during the visit. The medication bottle will be returned to the patient so that they can take the last dose the same evening, with the medication being finally returned to the site at the same time and using the same method (delivery by patient or collection by courier/ site staff) as the ACM. Compliance will be checked again when the bottle is returned.

8.7.5 Wash-out Period

At the end of Treatment Period A subjects will enter a washout period during which they will not take study medication. Subjects will, however, continue to complete the IPF Coughing Severity, additional cough severity, and other symptom scales in the eDiary each day.

The nominal washout period duration will be 21 days although it may be varied by up to ±3 days to accommodate subject and clinic schedules.

8.7.6 Visit 5 (End of Wash-out / Start of Treatment Period B)

This visit occurs at the end of the wash-out period and the start of Treatment Period B. The following assessments and procedures will be undertaken at the clinic site or during a home visit:

- Vital signs
- Spirometry
- 12-lead ECG
- Safety labs: blood samples for clinical chemistry and hematology and urine sample for urinalysis
- Blood sample for biomarkers
- Blood sample for orvepitant concentration
- Subjects will be asked to complete the study questionnaires: GRS and GRC, LCQ, K-BILD, PROMIS SD SF8b and HADS
- A review of changes in concomitant medications and any changes in health status (AEs)

The subjects will undergo re-training on the use of the diary, if required, and will be reminded of the need to continue to record the IPF Coughing Severity, additional cough severity, and other symptom scales in the eDiary daily for the next 4 weeks.

Study medication for Treatment Period B will be dispensed and the subject instructed to begin taking it the evening of the following day (to align with the start of treatment in Treatment Period A).

8.7.7 Visit 7

Visits 7 should be scheduled 28 (±3) days after Visit 5. The following assessments and procedures will be undertaken at the clinic site or during a home visit:

- Vital signs
- Spirometry
- 12-lead ECG
- Safety labs: blood samples for clinical chemistry and hematology and urine sample for urinalysis
- Blood sample for biomarkers
- Blood sample for orvepitant concentration
- Subjects will be asked to complete the study questionnaires: GRS and GRC, LCQ, K-BILD, PROMIS SD SF8b, HADS and HARQ
- The subject will be fitted with an ACM, which will be initiated prior to the subject leaving the clinic to monitor cough frequency over the next 24 hours. Immediately after the end of this period the subjects will either return the ACM to the clinic or arrangements will be made to collect it from the subject.
- A review of changes in concomitant medications and any changes in health status (AEs)

The subject will be instructed that they should record the IPF Coughing Severity, additional cough severity, and other symptom scales in the eDiary for the final time that evening and then return the device to the site at the Follow up visit.

Study medication compliance for Treatment Period B will be checked during the visit. The medication bottle will be returned to the patient so that they can take the last dose the same evening, with the medication being finally returned to the site at the same time and using the same method as for the ACM. Compliance will be checked again when the bottle is returned.

8.7.8 Visit 8

Visit 8 is the follow up / early termination visit for the study. It should be scheduled for 14 (±3) days after Visit 7 or at the earliest opportunity if the subject withdraws early.

The following assessments and procedures will be undertaken at the clinic site or during a home visit:

- Vital signs
- Symptom directed physical examination
- Spirometry
- 12-lead ECG
- Safety labs: blood samples for clinical chemistry and hematology and urine sample for urinalysis
- Global ratings of cough status and change
- A review of changes in concomitant medications and any changes in health status (AEs)

9. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

9.1 Selection of doses in the study

Two doses of orvepitant have been selected for evaluation in this study. The higher dose (30 mg once daily) is anticipated to be a fully effective dose based on findings from previous studies, notably the VOLCANO-2 study in patients with RUCC and the two Phase 2 studies in major depressive disorder. Additionally, this dose has a good safety and tolerability profile in the clinical studies completed to date (with more than 350 human subjects having received at least one dose at this level) and modelled data using the positron emission tomography Phase 1 study (NKG10002) findings indicates that full (≥99%) central NK_1 receptor occupancy will be achieved throughout the dose interval in >95% of subjects with 30 mg once daily.

The lower dose (10 mg once daily) shows good pharmacokinetic separation from the 30 mg dose and was effective in some assessments in the VOLCANO-2 study but compared to the 30 mg dose, the effects were inconsistent. This may reflect that central receptor occupancy would be at least 90% throughout the dose interval in ≥95% of subjects, a figure which may be insufficient for full efficacy. This lower dose has been included to enable a comparison to be made between a dose which is expected to be fully effective and one that is anticipated to have some efficacy but may be sub-optimal.

IPF is a rare disease and patients with troublesome cough are a sub-set of the population. Consequently, studying multiple doses to establish a full dose-response profile is not considered to be feasible in this population.

9.2 Investigational medicinal product

The IMP will consist of orvepitant 10 mg and 30 mg (free base equivalents) tablets or matching placebo. The tablets are white, film-coated round tablets containing orvepitant as the maleate salt or matching placebo to be taken orally once-daily.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

The physical, chemical, pharmaceutical formulation properties and characteristics of the IMP are described in the IB.

IMP (i.e., orvepitant 10 mg, orvepitant 30 mg or placebo) will be provided in white, opaque, high density polyethylene bottles with white opaque, child-resistant closures that include induction seal liners. A desiccant is also included in the bottle. Bottles will contain 34 tablets (enough for a 28-day dosing period plus overage).

The IMP bottles will be labelled in accordance with regulatory requirements for participating countries.

All IMP must be stored in a secure area with access limited to the Investigator and authorized site staff. The IMP is to be stored at ambient room temperature up to a maximum of 30°C.

Only authorised investigational site study staff members are to dispense the IMP.

9.3 Allocation to Treatment

The IMP each subject receives will be allocated by an IWRS tool provided by [redacted] on behalf of the Sponsor.

The study will be conducted in a double-blind manner, with the subjects, Investigators and Sponsor all blinded to the treatment allocated. Both orvepitant (10 mg and 30 mg) and placebo will be presented as white tablets, identical in size and shape.

Following the Screening period and confirmation of eligibility, subjects will be randomised in a 1:1 ratio to either Cohort 1 or Cohort 2, and then further randomised in a 1:1 ratio to receive either placebo in Treatment Period A or orvepitant in Treatment Period A.

9.4 Study Treatment and Administration

IMP will be taken once daily. IMP doses are fixed and will not be adjusted for individual subjects during the study.

At each visit (where appropriate, see Section 8.7) subjects will be dispensed IMP for self-administration for daily dosing until the subsequent visit, with overage included to allow for visit windows. An interim check of compliance will be made at all in person study visits (as appropriate).

Subjects will be required to take one tablet of IMP once-daily in the evening before retiring to bed. The study medication may be taken with or without food.

9.4.1 Missed dose

All doses are to be taken at approximately the same time each evening. If a subject forgets to take a dose in the evening it may be taken any time up until 9 am the following morning. After this time the dose should not be taken, and it will be considered a missed dose.

9.4.2 Dose interruption

If a subject experiences an AE which the investigator believes is treatment related and which the subject finds intolerable, a break in dosing of up to 1 week is permitted. If on reintroduction of the IMP, the AE recurs and remains intolerable the IMP will then be withdrawn altogether. A break in dosing will not result in extension of the overall dosing period.

9.5 Duration of Subject Participation

The total planned duration of participation in the study for an individual subject is up to 17 weeks, which comprises the following:

- Initial Screening phase of up to four weeks (excluding any additional periods for washout of prohibited concomitant medications)
- 4 weeks each for Treatment Periods A and B
- 3 weeks for the wash-out period
- 2 weeks for follow up

9.6 Treatment Accountability and Compliance Checks

In accordance with regulatory requirements, the Investigator or designated site staff must document the amount of IMP dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to the Sponsor (or representative) when applicable. IMP accountability records must be maintained throughout the course of the study. The

accountability unit for this study is a tablet. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused IMP will be provided.

The Investigator has overall responsibility in ensuring that the study treatment is received and managed at the study site in accordance with Good Clinical Practice (GCP).

Limited responsibility may be delegated to a nominated study site representative and this delegation must be documented. Study treatment will be dispensed by a nominated person at each study site.

The Sponsor will be permitted upon request to audit supplies, storage and dispensing records and procedures.

Every effort should be made to encourage subject compliance with the dosage regimen as per the protocol. All subjects will be instructed to return their medication bottle with any unused tablets at each visit. A record of the tablets dispensed, taken, and returned will be recorded at each visit and compliance calculated.

9.7 Treatment Blinding Code

Study investigators will be given access to the IWRS system for the purposes of emergency unblinding. The IWRS will be incorporated within the eCRF. Investigators are permitted to unblind treatment for a subject if it is deemed that knowledge of the subject's treatment will impact subject's future medical care. If possible, the medical monitor or Sponsor medical expert should be notified prior to the blind being broken. If this is not possible, the medical monitor or Sponsor medical expert must be notified as soon as possible if a code break was performed.

If a suspected unexpected serious adverse reaction (SUSAR) occurs that requires expedited reporting to the relevant regulatory agencies and Institutional Review Board (IRB) /Independent Ethics Committee (IEC), then the blind will be broken for the relevant subject by the Bionical Emas safety group before reporting. A blinded copy of the report will be provided to the investigators.

If unblinding occurs accidentally this will be considered a protocol deviation. It must be documented in the subject's medical notes and in the trial master file (TMF), and the Sponsor must be informed.

9.8 Permitted Concomitant Medications

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information, and dates of administration. Any medication that is not specifically prohibited is allowed.

Throat or cough lozenges (also known as a candies, drops, sweets or pastilles) and mucolytic agents are permitted.

9.9 Prohibited Concomitant Medications

A list of prohibited concomitant medications is provided in Appendix 1.

Due to their potential effect on cough reflex sensitivity, the use of opioids, dextromethorphan, gabapentin, pregabalin, baclofen, antihistamines, thalidomide, benzonatate or tricyclic antidepressants (e.g. amitriptyline) for treatment of cough is not allowed throughout the study (through to Visit 8). Subjects must have discontinued these drugs at least 4 weeks prior to the Baseline visit and should not have them started during the study. Subjects may, however, be permitted to continue to use these drugs if they have been prescribed solely for the management of another disorder (eg neuropathic pain, depression) and the dose has been stable for at least 1 month prior to screening.

Angiotensin converting enzyme (ACE) inhibitors are not allowed within 3 months of Screening and throughout the study.

The use of other NK_1 antagonists (e.g., aprepitant, fosaprepitant, rolapitant) is not permitted for any reason from 4 weeks before the Baseline visit until completion of Visit 8

Strong or moderate inhibitors of CYP3A4 are excluded from the day of Visit 2 until one week after the last dose of IMP in the study.

The following classes of medication are excluded from Screening until one week after the last dose of IMP in the study:

- Strong or moderate inducers of CYP3A4 (including but not limited to rifampicin, carbamazepine, efavirenz, bosentan, modafinil, St. John's Wort)
- Strong or moderate inhibitors of P-glycoprotein inhibitors

9.10 Other Study Restrictions

9.10.1 Driving and Operation of Machinery

Somnolence and dizziness have been identified as non-serious adverse reactions to orvepitant. Subjects will be instructed neither to drive nor operate machinery if they experience somnolence or dizziness.

9.10.2 Contraception

Female subjects of childbearing potential are excluded from the study and hence there are no contraceptive requirements for them.

Male subjects who are sexually active with a female partner of child-bearing potential (i.e., the partner is not surgically sterilised or postmenopausal) must agree to use a condom for the duration of participation in the study and for 30 days after the last dose of study medication.

10. STUDY SCHEDULE

Table 2: Schedule of Events

	Screening Visit	Baseline	Treatment Period A		End of Wash-Out / Start of Period B	Treatment Period B		Follow-up/ Early Termination[b]
			Week 2[f]	Week 4		Week 2[f]	Week 4	
Visit (V) Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Timing of visit	Within 14 to 28 days of V2	Day 0	14 days after V2	28 days after V2	21 days after V4	14 days after V5	28 days after V5	14 days after V7
Allowable window	N/A	0	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed Consent[a]	X							
Medical History & demographics	X							
Physical examination	X	X[c]						X[c]
Pulmonary function tests (spirometry)	X[j]	X		X	X		X	X
Inclusion/exclusion criteria	X	X[d]						
Concomitant medication review	X----------							----------X
Vital signs[e]	X	X		X	X		X	X
12-lead ECG	X	X		X	X		X	X
AE recording		X----------						----------X
Issue eDiary/Training/Compliance check	X	X	X	X	X	X		
Randomisation		X						
eDiary completion (once daily)[i]	X----------							----------X
Study drug dispensing/training		X			X			
Study drug collection/compliance check				X			X	
Ambulatory cough monitoring		X		X			X	
Daily dosing (evening before bed)			X[h] ---------- X			X[h] ---------- X		
Leicester Cough Questionnaire		X		X	X		X	
Hull Airway Reflux Questionnaire		X		X			X	
K-BILD Questionnaire		X		X	X		X	
PROMIS SF SD 8b		X		X	X		X	
Hospital Anxiety and Depression Scale		X		X	X		X	
Global ratings of status/change in cough		X[g]	X	X	X	X	X	X
Biomarker samples		X		X	X		X	
Clinical chemistry and haematology	X	X		X	X		X	X
Blood sample for orvepitant concentration				X	X		X	
Urinalysis	X	X		X	X		X	X

[a]	Informed consent will be obtained prior to any screening procedures being performed. Consent can be obtained prior to the Screening Visit or at the actual visit.
[b]	An Early Withdrawal/Safety Follow-up visit will be performed if the subject withdraws after the Baseline visit. This visit will consist of the same assessments as the Follow-up visit and should be scheduled within 14 days of the early termination date or discontinuation of investigational product.
[c]	Symptom directed examination, if required.
[d]	Any changes that may impact eligibility are reviewed
[e]	Systolic and diastolic blood pressure, pulse rate, temperature, arterial oxygen saturation (measured using a pulse oximeter). In addition, weight is recorded at visits 2 and 8.
[f]	These visits will be conducted remotely/virtually (by phone or videoconference)
[g]	At Baseline only the global rating of status is recorded
[h]	Starting the evening of the day following the Baseline and End of Wash-out Visits (to allow for completion of ambulatory cough monitoring at Baseline). Finishing the evening of the Week 4 visit.
[i]	Used to record IPF Coughing Severity Scale, additional cough scales and other symptom scale scores. Last day of completion is the evening of Visit 7.
[j]	At screening, DLCO also measured if required

10.1 Efficacy Assessments

10.1.1 IPF Coughing Severity Scale

The IPF Coughing Severity Scale is a numerical rating scale (NRS) which will be completed in the eDiary during the study, starting at Visit 1 and continuing through to the day of Visit 7. It will be completed once a day by the subject, in the evening, just before retiring to bed.

Subjects are asked to rate the severity of their coughing in the past 24 hours using an 11-point scale ranging from 0 (no coughing) to 10 (coughing as bad as you can imagine) (Appendix 2).

The eDiary will have a reminder function and will include a time window during which completion is permitted. On expiry of the window the assessment will be locked and if it hasn't been completed will be considered missing for that day.

Daily scores will be transferred from the eDiary provider's [redacted] database to [redacted] for statistical analysis. Scores will be averaged over 7-day periods to provide weekly average IPF Coughing Severity Scale scores for each assessment timepoint. A minimum of 4 daily assessments will be required for a valid weekly average.

10.1.2 Additional Cough Scales

10.1.2.1 Early morning cough scale

The early morning cough scale will be completed in the eDiary during the study in the same manner as the IPF Coughing Severity Scale.

Subjects are asked to rate the severity of their coughing first thing that morning on waking or rising using an 11-point NRS ranging from 0 (no coughing) to 10 (coughing as bad as you can imagine) (Appendix 2).

10.1.2.2 Rest of the day cough scale

The rest of the day cough scale will be completed in the eDiary in the same manner as the IPF Coughing Severity Scale.

Subjects are asked to rate the severity of their coughing during the rest of the last 24 hours (excluding the coughing first thing on waking) using an 11-point NRS ranging from 0 (no coughing) to 10 (coughing as bad as you can imagine) (Appendix 2).

10.1.3 Other Symptom Scales

10.1.3.1 Urge to Cough Scale

The urge to cough scale will be completed in the eDiary during the study in the same manner as the IPF Coughing Severity Scale.

Subjects are asked to rate the severity of their urge to cough in the past 24 hours using an 11-point NRS ranging from 0 (no urge to cough) to 10 (urge to cough as bad as you can imagine) (Appendix 2).

10.1.3.2 Cough Frequency Scale

The cough frequency scale will be completed in the eDiary during the study in a similar manner to the IPF Coughing Severity Scale.

Subjects are asked to rate the frequency of their coughing in the past 24 hours using a 5-point verbal rating scale ranging from Never to All the time (Appendix 2).

10.1.3.3 Dyspnoea Scale

The dyspnoea scale will be completed in the eDiary during the study in the same manner as the IPF Coughing Severity Scale.

Subjects are asked to rate the severity of their shortness of breath in the past 24 hours using an 11-point scale ranging from 0 (no shortness of breath) to 10 (shortness of breath as bad as you can imagine) (Appendix 2).

10.1.4 Global Rating of Status Questionnaire for Cough Severity

The global rating of status questionnaire comprises three questions that subjects will complete at Visits 2, 3, 4, 5, 6, 7 and 8

Subjects will be asked to rate the overall severity of:

- All coughing
- Coughing first thing in the morning
- Any other coughing

over the past week as either none, mild, moderate, severe or very severe (Appendix 3).

It will be completed during the study visit by the subject directly onto a tablet device except at visits conducted remotely in which the subjects' verbal rating will be transcribed onto the tablet by a member of the site staff.

10.1.5 Global Rating of Change Questionnaire for Cough Severity

The global rating of change questionnaire comprises three questions that subjects will complete at Visits 3, 4, 5, 6, 7 and 8

Subjects will be asked to rate the overall change in severity since starting the study of:

- All coughing
- Coughing first thing in the morning
- Any other coughing

They will select one of 7 responses that range from very much worse through no change to very much better (Appendix 3).

It will be completed during the study visit by the subject directly onto a tablet device except at visits conducted remotely in which the subjects' verbal rating will be transcribed onto the tablet by a member of the site staff.

10.1.6 Ambulatory Cough Monitor

Subjects will be fitted with an ACM (the Leicester Cough Monitor[10] [LCM]) to record cough frequency over 24 hours at Visits 2, 4 and 7.

The LCM will be started prior to the subject leaving the clinic to monitor cough frequency over 24 hours. After this period, the subjects will either return the monitor to the clinic or collection from the subjects will be organised. Cough frequency will be determined by a central evaluation service

[10] Intellectual property rights to the Leicester Cough Monitor owned by Professor Surinder Birring and King's College Hospital NHS Foundation Trust

(Department of Respiratory Medicine, Kings College Hospital, London, UK [Kings]) using standardised methodology and with appropriate quality control processes.

On the three occasions that cough frequency is assessed, patients will be provided with a paper form on which they will record the times during the recording period that they were asleep.

Analysed data will be transferred to [redacted] for statistical analysis. Kings will be provided with subject identifier information but will not have access to the randomisation code.

10.1.7 Leicester Cough Questionnaire

The LCQ is a 19-item questionnaire that assesses cough-related Quality-of-Life. It has three domains (physical, psychological and social). The total score range is 3-21 and domain scores each range from 1-7; a higher score indicates a better Quality-of-Life (Appendix 4).

Subjects will complete the LCQ during Visits 2, 4, 5 and 7.

It will be completed during the study visit by the subject directly onto a tablet device.

10.1.8 Kings Brief Interstitial Lung Disease (K-BILD) Health Status Questionnaire

The K-BILD is a brief, validated, self-completed health status measure for interstitial lung diseases. It comprises 15 questions in three domains (psychological, breathlessness and chest symptoms, Appendix 5). The recall period is 2 weeks. It will be completed by the subject at Visits 2, 4, 5 and 7.

It will be completed during the study visit by the subject directly onto a tablet device.

10.1.9 PROMIS SD SF 8b

The PROMIS (Patient-Reported Outcomes Measurement Information System, part of the National Institutes of Health Roadmap initiative designed to improve PROs using state-of-the-art psychometric methods) SD SF 8b is a short form questionnaire to assess sleep disturbance (Appendix 6). It comprises eight questions and will be completed by subjects at Visits 2, 4, 5 and 7.

It will be completed during the study visit by the subject directly onto a tablet device.

10.1.10 Hospital Anxiety and Depression Scale

The HADS is a widely used tool for assessing anxiety and depression in a general population. It comprises 14 questions, seven each for anxiety and depression, (Appendix 7) and will be completed by subjects at Visits 2, 4, 5 and 7.

It will be completed during the study visit by the subject directly onto a tablet device.

10.1.11 Hull Airway Reflux Questionnaire

The Hull Airway Reflux Questionnaire is a 14-item questionnaire that assesses airway hypersensitivity, particularly that associated with reflux of gastric contents (Appendix 8). It will be completed at Visits 2, 4 and 7.

It will be completed during the study visit by the subject directly onto a tablet device.

10.2 Safety Assessments

10.2.1 Medical history and concomitant diseases

A review of medical and medication history will be performed at Screening to confirm subject eligibility. This must be reviewed and by the investigator or a medically qualified sub-investigator. All medically relevant information should be recorded, regardless of the time since the date of diagnosis.

History should include (but not be limited to):

- All medications currently being taken, and any other medications taken within six months before the Screening Visit
- The date of diagnosis of IPF, which should be consistent with the requirements of the 2018 or 2022 joint ATS/ERS/JRS/ALAT Clinical Practice Guideline, and the date of onset of the subject's chronic cough
- Any other respiratory disorders
- Relevant medical history relating to cardiac, vascular, neurological, gastrointestinal, renal, hepatic, psychiatric disorders, and any other diseases.

10.2.2 Physical examinations

A full physical examination will be conducted at the Screening visit and a symptom directed physical examination at other visits, as shown in the Schedules of Events (Table 2). This will be completed by a physician or an appropriately qualified delegate.

A full physical examination is composed of a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose and throat
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological

Any abnormalities that are identified at the Screening Visit will be documented on the medical history eCRF page. Any changes (including new and worsening findings) between the Screening Visit and final study visit should be documented in the subject's source notes and recorded as AEs on the AE eCRF page.

If an improvement/resolution of a physical examination finding documented in the subject's medical history occurs during the study, it should be recorded in the subject's source notes. If there is resolution of a physical examination finding previously noted as an AE, then the event resolution and stop date should be recorded on the AE eCRF page and documented in the subject's notes.

10.2.3 Pulmonary function

Lung function will be assessed by spirometry in accordance with the joint 2019 American Thoracic Society and European Respiratory Society Technical Update on Standardization of Spirometry.[11] Measurements will be made and assessed locally at the study sites. The same model of spirometer should be used throughout the study for any given subject.

Spirometry will be performed at Visits 1, 2, 4, 5, 7 and 8.

Where possible (recognising that patients with IPF often find spirometry challenging), the highest values from three technically satisfactory attempts will be recorded and used for the purpose of eligibility. If three technically satisfactory attempts cannot be completed by the subject, the best attempt should be used.

Short acting bronchodilator agents should be withheld for at least 12 hours before a spirometry assessment and long acting bronchodilator agents should be withheld for at least 24 hours.

10.2.4 12-Lead ECGs

Resting 12-lead ECG data will be recorded after the patient has rested for at least five minutes in a semi-recumbent position. The same model of ECG recorder should be used throughout the study for any given subject.

ECGs will be recorded Visits 1, 2, 4, 5, 7 and 8

ECG reports must be reviewed, signed, and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal findings and determine whether they are clinically significant. These assessments will be recorded in the eCRF, and clinically significant findings must also be reported as AEs in the eCRF.

10.2.5 Clinical chemistry

Blood for clinical chemistry assessments will be collected and sent to the central laboratory for analysis at Visits 1, 2, 4, 5, 7 and 8

The following clinical chemistry parameters will be assessed: sodium, potassium, glucose, urea/urea nitrogen, creatinine, creatine kinase, albumin, calcium, phosphate, bilirubin (total), alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, bicarbonate, magnesium, chloride, total protein. Subjects do not need to fast before clinical chemistry samples are taken.

Clinical chemistry test reports must be reviewed, signed, and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal results and determine whether they are clinically significant. Clinically significant findings must also be reported as adverse events in the eCRF.

10.2.6 Haematology

Blood for haematology assessments will be collected and sent to the central laboratory for analysis at Visits 1, 2, 4, 5, 7 and 8.

[11] Graham B, Steenbruggen I, Miller M, Barjaktarevic I, Cooper B, Hall G, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019;200,e70–e88.

The following haematology parameters will be assessed: red blood cell count, white blood cell count, haematocrit, haemoglobin, mean cell volume, platelet count and white cell differentials.

All haematology test reports must be reviewed, signed, and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal results and determine whether they are clinically significant. Clinically significant findings must also be reported as adverse events in the eCRF.

10.2.7 Urinalysis

Urine for urinalysis assessments will be collected and sent to the central laboratory for analysis at Visits 1, 2, 4, 5, 7 and 8.

Parameters to be measured will comprise glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrites, leucocyte esterase, sedimentation.

Urinalysis test reports must be reviewed, signed, and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal results and determine whether they are clinically significant. Clinically significant findings must also be reported as adverse events in the eCRF.

10.2.8 Vital signs

Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, arterial oxygen saturation [SpO2]) will be measured at Visits 1, 2, 4, 5, 7 and 8.

Blood pressure will be measured using a standardised process:

- Subject should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level
- Use an automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery
- Measure and record the blood pressure using the same arm throughout the study

SpO2 will be measured using a pulse oximeter.

Additionally, weight will be measured at Visits 2 and 8.

All measurements are to be recorded on the Vital Signs eCRF.

All vital signs must be reviewed by the Investigator or delegated physician. The Investigator will comment on all abnormal results and determine whether they are clinically significant. These assessments will be recorded in the eCRF, and clinically significant findings must also be reported as adverse events in the eCRF.

10.3 Biomarkers

Serum/plasma will be collected for assessment of biomarkers at Visits 2, 4, 5 and 7.

Biomarkers to be assessed are:

Potential mechanistic / pharmacodynamic markers	• Monocyte chemo-attractant protein–1 (MCP-1) • Interleukin (IL)-1β • IL-6 • IL-17A

Potential markers of disease progression	• C3M

10.4 Pharmacokinetic Assessments

A single 'spot' blood sample for analysis of plasma orvepitant concentrations will be collected at Visits 4, 5 and 7.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures will be provided in the Laboratory Manual.

10.5 Adverse events

10.5.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Adverse Drug Reaction

All AEs considered to be untoward and unintended responses to an IMP related to any dose should be considered adverse drug reactions. The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The phrase "responses to an IMP" means that a causal relationship between the IMP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Serious Adverse Event (SAE)

An adverse event that:

- Results in death
- Is life-threatening (i.e., the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (see explanation below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered to be an important medical event

Based upon medical and scientific judgment, important medical events that may not be immediately life-threatening, or result in death or hospitalisation, but may jeopardize the subject and/or[12] may require intervention to prevent one of the other outcomes listed in the definition above may be considered a SAE.

[12] The definition varies between regulatory jurisdictions

Hospitalisations are defined as initial or prolonged admissions that include an overnight stay. Hospitalisation or prolonged hospitalisation for technical, practical, or social reasons, in the absence of an adverse event is not an SAE and neither is attendance at an Emergency Room / Accident and Emergency Department that takes place in the evening or night and does not result in formal admission to the hospital.

Adverse Events of Special Interest

For the purposes of this study, any "respiratory decline" event that doesn't meet the definition of an SAE is to be considered an adverse event of special interest (AESI) and should be reported by the investigator to the Sponsor in an expedited manner by completing the AESI form and sending it by email to the medical monitor. This will enable the Sponsor to monitor for potentially relevant safety findings that do not meet the definition of serious. Non-serious respiratory decline events include (but are not limited to) the following:

- Unscheduled visits to a healthcare professional for respiratory status deterioration.
- Urgent care visit for respiratory status deterioration.

In addition, any adverse event relating to suicidal ideation or suicidal behaviour that doesn't meet the definition of an SAE is to be considered an AESI and should be reported by the investigator to the Sponsor in an expedited manner by completing the AESI form and sending it by email to the medical monitor.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the reference safety information section of the current version of the Investigator's Protocol.

Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction may also constitute unexpected events.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse event that is suspected to be related to the administered medicinal product and the nature or severity of which is unexpected.

10.5.2 Assessment of Severity

The severity (intensity) of each adverse event will be classified as:

Mild	Awareness of sign or symptom, but easily tolerated by the subject
Moderate	Sign or symptom causes discomfort, but does not interfere with the subject's normal activities
Severe	Sign or symptom of sufficient intensity to interfere with subject's normal activities

10.5.3 Assessment of Causality

A determination will be made of the relationship (if any) between an AE and the study drug. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug. AEs will be classified as either related or unrelated.

10.5.4 Adverse Event Reporting

Adverse events may be volunteered spontaneously by the subject, or discovered as a result of general, non-leading questioning. Adverse events occurring from the Screening Visit up to the final

study visit will be recorded. All AEs should be recorded in the eCRF and in the subjects' source notes.

Any SAE occurring from the time the Screening Visit until 30 days after the last dose of IMP must be reported immediately (within 24 hours of the investigator becoming aware of it) and recorded on the SAE Form. Detailed instructions for the reporting of SAEs will be provided. All subjects with an SAE must be followed up and the outcomes reported. The investigator must supply the Sponsor and the relevant regulatory and ethics authorities with any additional requested information (e.g., autopsy reports and terminal medical reports). Any follow-up information on a previously reported SAE will also be reported within 24 hours of awareness.

If the Investigator does not have all information regarding an SAE, he/ she will not wait to receive additional information before reporting the event and completing the appropriate data collection form. The Investigator will always provide a preliminary assessment of causality at the time of the initial report as described in Section 10.5.3.

The primary mechanism for reporting SAEs will be a paper collection form.

'Scan & email' of the SAE form is the preferred method to transmit this information to the project contact for SAE receipt although fax transmission is also acceptable. In rare circumstances and in the absence of email capability or fax equipment, notification by telephone is acceptable, with a copy of the SAE data collection form sent by overnight mail. Initial notification via the telephone does not replace the need for the Investigator to complete and sign the SAE data collection form within the designated reporting periods.

NeRRe is required to expedite to regulatory authorities reports of SUSARs in line with the relevant legislation. Fatal or life-threatening SUSARs must be reported within 7 calendar days and other SUSARs within 15 calendar days.

All investigators will receive a safety letter notifying them of relevant SUSAR reports. If required by local reporting regulations, each Investigator must then notify his or her relevant Institutional Review Board (IRB) or Research Ethics Committee (REC). NeRRe will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

10.6 Pregnancy

Male subjects who are sexually active with a female partner of child-bearing potential must agree to use a condom for the duration of participation in the study and for 30 days after the last dose of study medication.

However, if the partner of a male study subject becomes pregnant during the subject's participation in the study and for up to 30 days after the last dose of IMP, this should be reported to the investigator. Consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

10.7 Data Safety Monitoring Board

A DSMB will be convened with the primary remit of providing independent safety oversight of the study. The composition of the DSMB, its terms of reference and its operating procedures will be described in the DSMB Charter which will be finalised before the first subject is randomised into the study.

The DSMB may, at any time, make recommendations to the NeRRe Chief Medical Officer of changes to the conduct of the study, including temporary or permanent discontinuation of the trial, to ensure the benefit-risk balance to participants remains appropriate. The default assumption is

that DSMB recommendations will be implemented by the Sponsor, although exceptionally there may be further consultation with third parties (for example regulatory agencies) before changes to study conduct are implemented.

11. STATISTICAL CONSIDERATIONS

11.1 General Statistical Considerations

Subjects will be randomised to cohort and then further randomised to treatment order.

The primary objective of the study is to evaluate the effect of orvepitant once daily on cough severity, as perceived by patients, with IPF. The corresponding primary endpoint is the mean change from Baseline to Week 4 (the last 7 days of treatment) in weekly average of the daily IPF Coughing Severity Scale score.

The primary objective will be assessed by testing the following hypotheses for each orvepitant dose group separately:

Null hypothesis (H0): There is no difference in the mean change in mean IPF Coughing Severity Scale scores for the orvepitant treatment group compared to placebo.

H0: μ (active) = μ (placebo)

Alternative hypothesis (H1): There is a difference in the mean change in mean IPF Coughing Severity Scale scores for the orvepitant treatment group compared to placebo.

H1: μ (active) $\neq$ μ (placebo)

Each comparison will be carried out at the two-sided 5% level of statistical significance. No adjustment will be made for the multiple orvepitant versus placebo group comparisons in this phase 2 study (two in total: 10 mg versus placebo, 30 mg versus placebo) as each dose cohort is tested independent (versus the corresponding placebo) and each is adequately powered.

11.1.1 Definition of Baseline

Baseline values will be defined separately for each treatment period, unless stated otherwise.

For the primary efficacy endpoint, period-specific baseline will be used in the analysis, which is the average of the 7 calendar days up to and including the date of Visit 2 for Treatment Period A and the average of 7 calendar days up to and including the date Visit 5 for Treatment Period B.

For secondary efficacy endpoints related to change from baseline, the period-specific baseline will be used when available; for those endpoints for which a period-specific baseline is not available (cough frequency and Hull Airway Reflux Questionnaire), the baseline in Treatment Period A will be used.

For safety assessments, baseline will be Visit 2 for Treatment Period A and for Treatment Period B it will be Visit 5.

For both safety and efficacy assessments, if the period-specific baseline is missing for Treatment Period A the value from Visit 1 will be used. If this is missing change from baseline will not be calculated. If the period-specific baseline is missing for Treatment Period B the value from Visit 2 (first preference) or Visit 1 (second preference) will be used. If both are missing change from baseline will not be calculated.

11.2 Carry Over Effects

A potential limitation of any cross-over study is the occurrence of confounding carry over effects between treatment periods. The wash-out period for this study is 3-weeks which, given that the half-life of orvepitant is approximately 33 hours, is expected to be sufficient for the drug to be fully cleared and for cough symptoms to return to baseline levels.

Period-specific baseline values will be used in the analysis of primary and secondary efficacy endpoints, and safety endpoints, when available, to protect against possible carryover effect.

11.3 Estimated Sample Size

Assuming a common standard deviation of 2.7 for the difference between treatment periods, a sample size of 40 subjects per cohort (18 -19 per sequence) has 90% power if the difference between treatments on the IPF Coughing Severity Scale is 1.5 points and assuming a two-sided type I error of 0.05, not adjusted for multiple comparisons. To allow for non-evaluable subjects/ missing data the withdrawal rate and extent of missing data will be monitored as the trial progresses and the actual sample size will be increased accordingly such that data is available for 37 evaluable subjects.

As there have been no previous studies using NRS for cough severity the standard deviation of 2.7 was obtained based on historical data of the change in cough severity measured using VAS. A 2-week observational study has since been completed in which the standard deviation of the change from baseline in NRS was 1.45 (95% CI: 1.14 - 2.01). Using the upper bound of the 95% CI and applying an inflation factor of 1.3 (derived from the observed increase in standard deviation from week 2 to week 12 in the historical VAS study data) resulted in an estimated standard deviation of 2.6. As this is very similar to, and lower than, the standard deviation originally used in the sample size estimation the estimated sample size required was not updated.

11.3.1 Sample size re-estimation

After at least 12 subjects in each cohort have completed Treatment Period B, the variance of the IPF Coughing Severity Scale data will be reviewed on a fully blinded basis. Additional subjects (up to a maximum of 10 per cohort) may be recruited if the emerging IPF Coughing Severity Scale data is found to have greater variance than allowed for in the original sample size estimate. Any possible impact on the type I error due to this blinded sample size re-assessment procedure is believed to be negligible [45].

11.4 Estimand

The primary **objective** of the study is to evaluate the efficacy of orvepitant as a treatment for chronic cough in patients with IPF.

The **treatment of interest** is orvepitant (at a dose of 10 or 30 mg once daily). The effects of orvepitant will be compared to placebo.

The **population** is patients with IPF and troublesome chronic cough in whom the cough is attributed to the IPF.

The main **variable** being used to assess the estimand is the IPF Coughing Severity Scale.

The estimand will be **summarised** by comparing the mean changes from baseline in weekly cough severity score for the orvepitant treatment period versus the placebo treatment period.

Intercurrent events that are expected to occur during the study are initiation of concomitant medication, withdrawal from study treatment, withdrawals from the study due to death.

A treatment policy strategy will be used for the initiation of concomitant medication as well as for early withdrawal from study treatment, essentially following the intention to treat principal. Any patients who discontinue treatment early will be followed up until the end of the study, with the aim of collecting all scheduled data.

A while on-treatment strategy will be used for withdrawal from the study due to death. All data for any subjects who die will be included up to the point of their withdrawal or death and no imputation will be made for any visits that may have occurred after the intercurrent event.

The estimand can then be defined as the difference between orvepitant and placebo in the change from baseline in weekly IPF Coughing Severity Scale score, measured using an NRS, in patients with IPF and troublesome chronic cough in whom the cough is attributed to the IPF, regardless of their need for concomitant medications or whether they discontinue study treatment, up until they complete the study, withdraw from the study or die (whichever comes first).

11.5 Analysis Sets

The following data sets will be used for the statistical analysis.

1. **Safety Set**: All subjects who receive at least one dose of double-blind study drug irrespective of treatment received. Subjects will be analysed according to treatment received
2. **Full Analysis Set (FAS):** All randomised subjects who received at least one dose of double-blind study drug, irrespective of treatment received, and have sufficient IPF Coughing Severity Scale data for at least one post-treatment assessment. Subjects will be analysed according to randomised treatment. This is the primary efficacy analysis set for the study.
3. **Per Protocol (PP) Set**: All subjects in the FAS excluding those identified as having a relevant protocol violation, where a relevant violation is one that potentially confounds the analysis of the primary efficacy endpoint.
4. **Exposure-Response (ER) Set:** all subjects who received at least one dose of double-blind study drug and for whom the PK data are considered sufficient.

Analysis Sets will be agreed at a blinded data review meeting prior to the unblinding of the study.

11.6 Data Analysis

Full details of the proposed statistical analyses will be documented in the SAP. In the event that text pertaining to statistical analysis differs between the SAP and protocol, the text in the SAP will take precedence.

Cohorts 1 and 2 will be analysed separately for efficacy.

For continuous data and for ordered categorical data, if appropriate, the number of non-missing observations, mean, standard deviation, geometric mean (where appropriate), median, first and third quartiles, minimum and maximum will be calculated. For ordered categorical data and nominal data, absolute counts, and relative frequencies (in %) will be calculated.

All statistical hypothesis tests and confidence intervals will be two sided, using a type I error rate of 0.05. No adjustment for multiple comparisons will be used for this study.

All raw data will be listed.

11.7 Demographics and Baseline Characteristics

Relevant Screening and Baseline data (i.e., data collected prior to the treatment administration) and demographic characteristics will be summarised descriptively for each treatment sequence and overall.

11.8 Statistical Methods for Efficacy Parameters

An analysis of covariance (ANCOVA) model will be used to assess the primary and secondary endpoints in the study. It is expected that the response variable will be the change from baseline in the mean score at the later time point of interest, and the predictor variables will be treatment, baseline mean score for each endpoint, treatment*period. Other covariates, such as age and sex, and their impact on the results may be done post-hoc. More details will be provided in the SAP.

Selected efficacy parameters will be summarised and analysed for the following sub-groups:

- By use of concomitant disease modifying therapies at Baseline (yes, no [nintedanib or pirfenidone])
- By IPF Coughing Severity Scale score at Baseline
- By cough frequency at Baseline

Other sub-groups (e.g., age, sex, ethnicity) will be evaluated if there are sufficient subjects to warrant analysis.

11.9 Statistical Methods for Safety Parameters

Safety data will be summarised descriptively for each treatment. No formal inferential tests will be performed on safety data.

The number of treatment emergent AEs (TEAEs), and subjects with TEAEs, will be compared between treatments. TEAEs are defined as AEs that first occurred or worsened in severity after the first dose of IMP.

TEAEs will be summarised for all causality AEs and for treatment-related AEs (those with related relationship to IMP and missing). TEAEs will be summarised by MeDRA body system and preferred term. TEAEs will also be reported by severity.

Any deaths, SAEs and AEs leading to discontinuation of IMP administration will also be summarised by treatment group.

SAEs will be presented in a similar way to AEs.

Vital signs will be summarised for each treatment group by visit. Summary statistics will be presented for absolute values and the change from Baseline.

ECGs will be assessed by the Investigator for abnormal findings. These will be categorised and summarised as normal, abnormal-not clinically significant, or abnormal-clinically significant. ECG intervals will be recorded and summarised as absolute values and changes from Baseline.

Clinical laboratory data for individual subjects will be listed and any out of range values will be highlighted. Laboratory data will be summarised for each treatment group by visit. Summary statistics will be presented for absolute values and change from Baseline, as well as an analysis of shifts from Baseline.

Extent of exposure and compliance will be summarised.

Selected safety parameters will be summarised for the following sub-groups:

- By use of concomitant disease modifying therapies at Baseline (yes, no [nintedanib or pirfenidone])

11.10 Pharmacokinetics Analysis

The plasma orvepitant concentrations will used to confirm individual subject exposure to orvepitant and to explore exposure differences in the two doses being evaluated. The data may also be analysed using a population pharmacokinetic (Pop PK) approach by nonlinear mixed effects modeling (NONMEM®). The Pop PK model will be used to evaluate the relationship between orvepitant exposure and clinical endpoints. The details of the analysis will be described in a Pop PK Data Analysis Plan and the data will be reported separately from the safety and efficacy findings.

11.11 Missing Data

Summary statistics will be based primarily on non-missing values, with no imputation of any missing data (as per the strategies for treatment for the intercurrent events outlined in Section 11.4). For hypothesis tests, estimates and confidence intervals, missing values for continuous efficacy endpoints analysed via likelihood methods (e.g., repeated measures mixed models) will not be directly imputed as they are handled within the analysis itself, under the assumption that the model specification is correct, and that the data is missing at random. Sensitivity analyses may be conducted to check the robustness of the analysis results under alternative assumptions with regards to missing data. Further details on the handling of missing values, including rules applied to incomplete questionnaires and any planned sensitivity analyses will be defined in the SAP.

12. END OF THE STUDY

The end of the study will be defined as the last subject's last visit.

13. ETHICS COMMITTEE REVIEW/INFORMED CONSENT

13.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Relevant Authorities

The final study protocol, the subject information and consent form and any other subject facing materials (e.g., questionnaires, advertisements) will be approved by an appropriately constituted IRB/IEC. Approval will be received in writing before initiation of the study.

Clinical study authorisation will be obtained prior to initiation of the study from the relevant Regulatory Authority.

13.2 Ethical Conduct of the Study

The study will be performed in accordance with the local regulations, the principals of Good Clinical Practice (GCP) as described by the International Council for Harmonization (ICH), and the ethical principles that have their origins in the Declaration of Helsinki.

13.3 Informed Consent

For each study subject, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the principal investigator or one of his/her associates will explain orally and in writing the nature, duration, purpose of the study, and the action of the study drug in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. They will be informed that their medical records may be reviewed by appropriately qualified monitors of the Sponsor or Sponsor Representative, and by auditors or regulatory authorities to ensure the accuracy of the details recorded as part of the study. They will be informed that they may withdraw from the study at any time without prejudice to further treatment. They will receive all information that is required by local regulations and ICH guidelines.

14. STUDY AND DATA MANAGEMENT

14.1 Protocol Amendments

Once approved by the applicable Regulatory Authorities and IRBs/IECs, the protocol must not be amended without approval by NeRRe. Unless an amendment is required to be implemented urgently in the interests of safety, or is deemed administrative by NeRRe, any amendments to the protocol must be authorised by the applicable Regulatory Authorities and IRB/IEC prior to implementation.

14.2 Monitoring

In accordance with applicable regulations including GCP and NeRRe or delegated CRO's Standard Operating Procedures (SOP), approved clinical research monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and NeRRe requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document. A list of what is to be classed as 'source documentation' will be documented in the Study Monitoring Plan.

NeRRe will monitor the study and sites to verify:

- Data are authentic, accurate and complete
- Safety and right of the subjects are being protected
- IMP accountability
- SAE reporting
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements

The investigator[s]/institution[s] will permit study-related monitoring, providing direct access to source data/documents.

14.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the investigator[s]/institution[s] will permit study-related audits, IRB/IEC review, and regulatory inspection[s], providing direct access to source data/documents.

14.4 Data Recording

14.4.1 Data to be Considered as Source Data

An eCRF will be used to capture subject data into a secure, validated database. Access to enter data in the eCRF will be limited to delegated and trained investigator site staff only. eDiary, tablet (for questionnaires), ACM and safety laboratory data will be transferred electronically into the database periodically during the study. PK and biomarker data will be transferred electronically into the database at study end.

Source data may be defined as information from an original record or certified copy of the original record containing patient information for use in the trial. The information may include, but is not limited, to clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified

copies) (ICH E2A Guideline). Examples of source data include subject identification and randomisation identification.

14.5 Confidentiality

The Investigator must assure that the subjects' anonymity will be maintained. On all study documentation, with the exception of the consent form and subject ID logs, subjects will only be identified by their unique identification code and will not be referred to by name.

Study data will be handled with utmost discretion within the context of physician's confidentiality. On the eCRFs and other study specific documents, subjects are not identified by their names, but by a unique subject number. Names of participating subjects and data generated as a result of this study will not be passed on to unauthorised persons.

The Investigator must assure that the subjects are properly anonymised throughout the study. On all study documentation which is intended to leave the site (i.e., to be transmitted to NeRRe, CRO or third parties), subjects will only be identified by their unique identification code and will not be referred to by name.

NeRRe may transfer some data collected during the study to a different company or regulatory authority outside of the US or EU for the purpose of processing, review, analysis or storage. Whenever the subject's personal data is transferred, it will be kept confidential and secure, and will used only for the purpose for which it was collected.

Safety and biomarker analysis samples collected during the study will be analysed at a central laboratory. Samples will be identified by the subjects' unique identification code. All safety samples will be destroyed after the assays have been completed.

Blood samples for analysis of orvepitant concentrations will be shipped to Aptuit Srl, Italy for analysis. Samples will be identified by the subjects' unique identification code. Following completion of the analysis, all samples will be destroyed.

14.6 Retention of Study Data

Following closure of the study, the Investigator must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/ regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the originals, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

NeRRe will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or NeRRe, or delegated CRO's SOPs; otherwise, the retention period will default to 25 years.

The Investigator must notify NeRRe of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the

Investigator leaves the site. The Investigator may not dispose of any records without prior approval from NeRRe.

14.7 Communication and Publication of Results

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report (CSR). The Investigator will be provided appropriate access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at NeRRe or another mutually agreeable location.

The original eCRFs and all data generated during the study under this protocol will become the property of the Sponsor.

Information about the study will be posted to a publicly available website such as (clinicaltrials.gov). Upon completion of the CSR, NeRRe will ensure public disclosure of the clinical trial research results according to NeRRe's SOP. A summary of the results will be posted to the public website.

It is the intent of all parties that the results of the study be published at an appropriate scientific conference and/or in a peer-reviewed journal in a timely manner consistent with academic standards and with due consideration given to the protection of intellectual property rights. The Chief Investigator and NeRRe will be responsible for assembling the proposed publication; this must happen with due diligence and with minimal delay.

Any proposed publication or presentation (including a manuscript, abstract or poster) initiated by an Investigator for submission to a journal or scientific meeting should be sent to the Sponsor for review at least sixty (60) days prior to submission. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. Sponsor may delay such submission by a maximum of six months if it reasonably believes that publication of results may compromise its intellectual property rights or else insist that such information or data is removed from the proposed publication. Publication of the results will not include confidential information without the permission of the Sponsor.

14.8 Indemnification

In the event of study-related damage or injuries, the clinical trial insurance of the Sponsor provides compensation for claims that arise in accordance with the regulatory requirements of the countries involved, except for claims that arise from willful misconduct or gross negligence. A copy of the country-specific insurance certificates will be held in the TMF and in the Investigator Site File.

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Principal Investigator Agreement

I agree to conduct the study according to the terms and conditions of this protocol, current Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signature: _____

Name of Principal Investigator:

Title:

Date:

17. APPENDICES

Appendix 1: Prohibited Concomitant Medications

Appendix 2: Numerical /verbal rating scales for cough severity, urge to cough, cough frequency and dyspnoea

Appendix 3: Global ratings of status and change in cough severity

Appendix 4: Leicester Cough Questionnaire

Appendix 5: Kings Brief Interstitial Lung Disease Questionnaire

Appendix 6: PROMIS SD SF 8b sleep questionnaire

Appendix 7: Hospital Anxiety and Depression Scale

Appendix 8: Hull Airway Reflux Questionnaire

17.1 APPENDIX 1: Prohibited Concomitant Medications

Prohibited for the periods shown	
Medications potentially confounding efficacy	Prescription Treatments Due to their potential effect on cough reflex sensitivity, the use of opioids, dextromethorphan, gabapentin, pregabalin, baclofen, antihistamines, thalidomide, benzonatate or tricyclic antidepressants (e.g. amitriptyline) is not permitted from 4 weeks before Visit 2 until completion of Visit 8. Subjects may, however, be permitted to continue to use these drugs if the dose has been stable for at least 4 weeks before Screening and they have been prescribed solely for the management of another disorder (e.g. neuropathic pain, depression). Immune-suppressant drugs and systemic corticosteroids taken for co-morbidities are permitted provided the dose has been stable for at least 2 weeks before the screening visit and they are expected to be used at this dose throughout the study. Any other use is prohibited. The use of other NK_1 antagonists (eg aprepitant, fosaprepitant, rolapitant) is not permitted for any reason from 4 weeks before the Baseline visit until completion of Visit 8. Angiotensin converting enzyme (ACE) inhibitors are not allowed within 3 months of Screening and throughout the study. Note: Throat or cough lozenges (also known as a candies, drops, sweets or pastilles) and mucolytic agents **are permitted**.
Prohibited from the day of Visit 2 until one week after the last dose of study medication	
Strong inhibitors of CYP3A4 (± P-glycoprotein)	atazanavir, boceprevir, cobicistat, clarithromycin, danoprevir and ritonavir, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole
Moderate inhibitors of CYP3A4	ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
Prohibited from the Screening visit until one week after the last dose of study medication	
Strong or moderate P-glycoprotein inhibitors	amiodarone, carvedilol, lapatinib, propafenone, quinidine, ranolazine

Strong inducers of CYP3A4	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
Moderate inducers of CYP3A4	bosentan, efavirenz, etravirine, phenobarbital, primidone

17.2 APPENDIX 2: Numerical / Verbal Rating Scales

IPF Cough Severity Scale

How severe was your coughing in the last 24 hours at its worst?

0	1	2	3	4	5	6	7	8	9	10
No coughing										Coughing as bad as you can imagine

Additional Cough Severity Scales

Early Morning Cough Scale

How severe was your coughing **first thing this morning** on waking or rising?

0	1	2	3	4	5	6	7	8	9	10
No coughing										Coughing as bad as you can imagine

Rest of the Day Cough Scale

How severe was **any other coughing** during the last 24 hours at its worst, excluding any coughing first thing this morning?

0	1	2	3	4	5	6	7	8	9	10
No coughing										Coughing as bad as you can imagine

Other Symptom Scales

Urge to Cough Scale

How severe was your **urge to cough** in the last 24 hours at its worst?

0	1	2	3	4	5	6	7	8	9	10
No urge to cough										Urge to cough as bad as you can imagine

Dyspnoea Scale

How severe was your **shortness of breath** in the last 24 hours at its worst?

0	1	2	3	4	5	6	7	8	9	10
No shortness of breath										Shortness of breath as bad as you can imagine

Cough Frequency Scale

How often did you cough in the last 24 hours? Select one answer

Never Rarely Sometimes Often All the time

17.3 APPENDIX 3: Patient Global Ratings

Patient Global Ratings of Status

GRS Question 1

Please select the response that best describes how severe **your coughing** was in the last week:

None, mild, moderate, severe, very severe

GRS Question 2

Please select the response that best describes how severe your coughing was **first thing in the morning** on waking or rising in the last week:

None, mild, moderate, severe, very severe

GRS Question 3

Please select the response that best describes how severe **any other coughing** was, excluding any coughing first thing in the morning, during the last week:

None, mild, moderate, severe, very severe

Patient Global Ratings of Change

GRC Question 1

Please select the response that best describes the change in **your coughing** since the start of the study:

-3	-2	-1	0	1	2	3
Very much worse	Somewhat worse	Slightly worse	No change	Slightly better	Somewhat better	Very much better

GRC Question 2

Please select the response that best describes the change in your coughing **first thing in the morning** on waking or rising since the start of the study:

-3	-2	-1	0	1	2	3
Very much worse	Somewhat worse	Slightly worse	No change	Slightly better	Somewhat better	Very much better

GRC Question 3

Please select the response that best describes the change in **any other coughing**, excluding any coughing first thing in the morning, since the start of the study:

-3	-2	-1	0	1	2	3
Very much worse	Somewhat worse	Slightly worse	No change	Slightly better	Somewhat better	Very much better

17.4 APPENDIX 4: Leicester Cough Questionnaire

Authors: Birring, S and Pavord, I.

Note: The version of the LCQ provided in this appendix is for information only and may differ slightly from the actual versions used on the study. A license to use the LCQ for the purpose of the study will be obtained prior to study start.

LEICESTER COUGH QUESTIONNAIRE

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

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Sometimes	Occasionally	Rarely	Never

3. In the last 2 weeks, have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

6. In the last 2 weeks, my cough has made me feel anxious

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

10. In the last 2 weeks, has your cough disturbed your sleep?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

11. In the last 2 weeks, how many times a day have you had coughing bouts?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	None

12. In the last 2 weeks, my cough has made me feel frustrated

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

13. In the last 2 weeks, my cough has made me feel fed up

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

15. In the last 2 weeks, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Sometimes when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

LCQ - United Kingdom/English - Mapi.

LCQ_AU1.1_eng-GBori.doc

17.5 APPENDIX 5: Kings Brief Interstitial Lung Disease Questionnaire

Note: The version of the K-BILD provided in this appendix is for reference only and may differ slightly from the actual versions used on the study. A license to use the K-BILD for the purpose of the study will be obtained prior to study start.

King's Brief ILD Questionnaire (K-BILD)

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

1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill.

1. Every time
2. Most times
3. Several Times
4. Some times
5. Occasionally
6. Rarely
7. Never

2. In the last 2 weeks, because of my lung condition, my chest has felt tight.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

3. In the last 2 weeks have you worried about the seriousness of your lung complaint?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

4. In the last 2 weeks have you avoided doing things that make you breathless?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

5. In the last 2 weeks have you felt in control of your lung condition?

1. None of the time
2. Hardly any of the time
3. A little of the time
4. Some of the time
5. A good bit of the time
6. Most of the time
7. All of the time

6. In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

8. In the last 2 weeks, my lung condition has made me feel anxious.

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

10. In the last two weeks how much of the time have you felt your lung disease is getting worse?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

12. In the last 2 weeks have you expected your lung complaint to get worse?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

14. In the last 2 weeks, has your lung condition made you think more about the end of your life?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

15. Are you financially worse off because of your lung condition?

1. A significant amount
2. A large amount
3. A considerable amount
4. A reasonable amount
5. A small amount
6. Hardly at all
7. Not at all

Thank you for completing this questionnaire

17.6 APPENDIX 6: PROMIS SD SF 8b Sleep Questionnaire

Note: The version of the PROMIS SD SF 8b provided in this appendix is for reference only and may differ slightly from the actual versions used on the study. A license to use the PROMIS SD SF 8b for the purpose of the study will be obtained prior to study start.

PROMIS Item Bank v1.0 – Sleep Disturbance – Short Form 8b

Sleep Disturbance – Short Form 8b

Please respond to each item by marking one box per row.

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep108	My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep115	I was satisfied with my sleep	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep116	My sleep was refreshing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Sleep87	I had trouble staying asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep90	I had trouble sleeping	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep110	I got enough sleep	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

		Very poor	Poor	Fair	Good	Very good
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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17.7 APPENDIX 7: Hospital Anxiety and Depression Scale

Note: The version of the HADs provided in this appendix is for reference only and may differ slightly from the actual versions used on the study. A license to use the HADS for the purpose of the study will be obtained prior to study start.

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

This edition first published in 1994 by nferNelson Publishing Company Ltd (now GL Assessment Ltd),1st Floor Vantage London, Great West Road, Brentford TW8 9AG

GL Assessment Ltd is part of the GL Education Group.

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17.8 APPENDIX 8: Hull Airway Reflux Questionnaire

Note: The version of the HARQ provided in this appendix is for information only and may differ slightly from the actual versions used on the study. A license to use the HARQ for the purpose of the study will be obtained prior to study start.

HULL AIRWAY REFLUX QUESTIONNAIRE

Please circle the most appropriate response for each question

Within the last MONTH, how did the following problems affect you? **0 = no problem and 5 = severe/frequent problem**						
Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
The feeling of something dripping down the back of your nose or throat	0	1	2	3	4	5
Retching or vomiting when you cough	0	1	2	3	4	5
Cough on first lying down or bending over	0	1	2	3	4	5
Chest tightness or wheeze when coughing	0	1	2	3	4	5
Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5)	0	1	2	3	4	5
A tickle in your throat, or a lump in your throat	0	1	2	3	4	5
Cough with eating (during or soon after meals)	0	1	2	3	4	5
Cough with certain foods	0	1	2	3	4	5
Cough when you get out of bed in the morning	0	1	2	3	4	5
Cough brought on by singing or speaking (for example, on the telephone)	0	1	2	3	4	5
Coughing more when awake rather than asleep	0	1	2	3	4	5
A strange taste in your mouth	0	1	2	3	4	5

TOTAL SCORE_____/70

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