Royal Brompton and Harefield

Guy's and St Thomas' NHS Foundation Trust

STUDY PROTOCOL

PAciFy Cough: A multicentre, double blind, placebo controlled, crossover trial of morphine sulfate for the treatment of PulmonAry Fibrosis Cough

Sponsor's R&D Registration Number: RBH2019/001
Sponsor's Details: Royal Brompton and Harefield Hospitals (RBHH), Guy's and St Thomas' NHS Foundation Trust (GSTFT)
EudraCT number: 2019-003571-19

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Signature Page and Statement

The Chief Investigator (CI) and the RO have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol except in the case of medical emergency (Section 15.10) or where departures from it may be mutually agreed in writing.

The Investigator agrees to conduct the trial in compliance with the protocol, GCP and UK Regulations for CTIMPs, the General Data Protection Regulation (GDPR), the Trust Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care Research, the Sponsor's SOPs, and other regulatory requirements as appropriate.

This protocol has been written in accordance to the Sponsor's procedure for writing study protocols outlining study procedures for the conduct and management of Clinical Trials of Investigational Medicinal Products (CTIMPs).

Chief Investigator (CI)		
Philip Molyneaux Consultant in Respiratory Medicine		
Royal Brompton and Harefield Hospitals (RBHH)	Signature	Date
Principal Investigator (PI) (if different from CI)		
Insert name and surname Insert job title		
Principal Investigator Site	Signature	Date
Sponsor Representative		
Ira Jakupovic Head of Research Governance and Regulatory Compliance		
Royal Brompton and Harefield Hospitals (RBHH)	Signature	Date

Contents

1 List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised
MA	Marketing Authorisation
Main REC	Main Research Ethics Committee
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MS	Member State
MUST	Malnutrition Universal Screening Tool
NHS R&D	National Health Service Research & Development
NIMP	Non- Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
RO	Research Office
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event

SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
WOCBP	Woman of Child bearing potential

2 Study personnel

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3 Study synopsis

Full study title:	A multicentre, double blind, placebo controlled, crossover trial of morphine sulfate for the treatment of PulmonAry Fibrosis Cough.
Short study title:	PaciFy Cough
IRAS ID number:	275034
Study drug:	1. Morphine sulfate 2. Placebo
Chief Investigator:	Dr Philip Molyneaux
Study centres/sites:	1. Royal Brompton Hospital (RBH) 2. Manchester University NHS Foundation Trust (MFT) 3. Aintree University Hospital NHS Foundation Trust.
Study duration:	24 months
Clinical phase:	Phase 3
Primary Objective:	To demonstrate that Morphine Sulfate reduces cough frequency in patients with IPF compared to placebo.
Secondary Objective:	To evaluate the within subject differences in self-reported and objective cough frequency with morphine compared with placebo therapy. To explore the relationships between quality of life, anxiety, dyspnoea and the response to morphine. To explore the relationship between activity and cough and the response to morphine. To evaluate a range of exploratory biomarkers for cough and response to Morphine Sulfate.
Study population:	44 patients
Methodology:	This is a randomised, double blind, placebo controlled, two-way crossover, multicentre study to assess the physiological effect of controlled release morphine sulfate (MST) on the urge to cough and objective cough counts in subjects with idiopathic pulmonary fibrosis (IPF).
Eligibility criteria:	***Inclusion criteria:*** **1.** Self-reported cough (> 8 weeks), with cough VAS ≥ 30/100 **2.** A diagnosis of IPF within 5 years prior to the screening visit, as per applicable ATS/ERS/JRS/ALAT guidelines, in line with hospital records. **3. Age** 3.1. Male and female participants aged ≥ 40 – 90 years at the time of signing informed consent **4. Sex:** 4.1 **Male participants**: A male participant must agree to use contraception as detailed in Appendix 2 of this protocol during the study and for at least 90 days after the follow-up visit, and refrain from donating sperm during this period 4.2 **Female participants**: A female participant is eligible to participate if she is not pregnant, not breastfeeding, and not a woman of childbearing potential (WOCBP) as defined in Appendix 2. **5.** Meeting all of the following criteria during the screening period: FVC ≥ 45% predicted of normal, Forced expiratory volume in 1 second (FEV1)/FVC ≥0.7, DLCO corrected for Hb ≥30% predicted of normal.

	Lung function performed within 12 months of the screening period is acceptable. **6.** The extent of fibrotic changes is greater than the extent of emphysema on the most recent HRCT scan (investigator determined within 24 months of the study screening visit) **7.** Written informed consent.
	Exclusion criteria: 1. Treatment with immunosuppressive therapy or antibiotics within last 4 weeks. A stable dose of corticosteroids equivalent to prednisolone of 10 mg per day or less, if used for an indication other than pulmonary disease will be permitted 2. Current smoker 3. History of alcohol and drug(s) addiction 4. Regular use of sedative therapies 5. Acute IPF exacerbation within 6 months prior to screening and/or during the screening period. 6. Concurrent use of pirfenidone or Nintedanib, unless receiving a stable dose for at least 8 weeks prior to screening 7. Use of ACE inhibitors 8. Patients with co-existent conditions know to be associated with the development of fibrotic lung disease. This includes: connective tissue disease, (plural plaques, mesothelioma), granulomatous disease including sarcoidosis. Patient with auto-immune profile considered diagnostic for a specific connective tissue disease will be excluded, even in the absence of systemic symptoms. Non-specific rises in auto antibodies *e.g.* rheumatoid factors, anti-nuclear antibody *etc.* will not be used to exclude individuals from the study. 9. Significant other organ co-morbidity including hepatic or renal impairment and pulmonary hypertension (investigator determined). 10. Significant coronary artery disease (myocardial infarction within 6 months or ongoing unstable angina within 4 weeks of screening visit) or congestive cardiac failure based on clinical examination 11. Patients as significant risk of side effects, intolerance or allergy to morphine 12. Pregnant and breastfeeding patients, or women or child-bearing potential, not using a reliable contraceptive method (see Appendix 2). A urine pregnancy test will be performed in females of child-bearing potential at the initial study visit. 13. Unable to provide informed written consent 14. Predicted life expectancy < 6 months 15. Use of long-term oxygen therapy. Use of ambulatory oxygen will be permitted. 16. Current or use of opiates within 14 days of the screening visit.
Study drugs, Dose and Mode of Administration:	
Morphine Sulphate (MST) 5mg twice daily given orally.	
Duration of Treatment:	28 days
Criteria for evaluation:	***Primary outcome variable:*** The percent change in daytime cough frequency (coughs per hour) from baseline as assessed by objective digital cough monitoring at Day 14 of treatment.
	Secondary outcome variables:

	1. Change from baseline in health-related quality of life scores (L-IPF, HADS, K-BILD) 2. Change from baseline in self-reported cough (LCQ & VAS) 3. Change from baseline in Dyspnoea (D12) 4. Change from baseline in global impression of change in quality of life, cough and breathlessness. 5. Proportion of responders with a minimum of 20% decrease from baseline at the end of treatment in 24-hour average cough count.

4 Introduction

4.1 Background

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, fibrotic lung disease of unknown cause (1). It is irreversible and responsible for 1 in every 100 deaths each year in the UK. Despite the recent approval of two antifibrotic therapies the 5-year survival rate remains 25%, far worse than many common cancers (2). While current therapies and those in development are understandably targeted at slowing the relentless progression of the disease none attempt to alleviate any of the significant symptoms that patients with IPF suffer from (3). The most common symptoms reported by patients are fatigue (95%), dyspnoea (88%) and cough (85%) (4). Cough can be a distressing symptom with significant physical, social and psychological consequences particularly anxiety and depression. The majority of patients with IPF report cough at some point during their disease (5) and it has been associated with a marked impairment in quality of life (6,7).

The pathogenesis of cough in IPF is poorly understood. Patients with IPF have been shown to have a more sensitive cough reflex compared to healthy controls – both in response to inhaled challenge agents and to mechanical stimuli (8). There is also a suggestion that genetic polymorphisms which contribute to the risk of developing IPF may also be implicated in IPF related cough (9). The lack of pathogenic clarity has limited the therapeutic options available to patients and clinicians and cough in IPF remains one of the most challenging symptoms to address. Thalidomide has been shown to be beneficial in a randomised control trial, however it's side effects profile renders it practically useless as only 20% of patients are able to tolerate it (10). Pirfenidone, one of the novel antifibrotic agents, has shown some promise in a recent trial (11) as has a nebulised form of sodium cromoglicate (12). The reduction in objective cough frequency demonstrated by the currently available drugs to treat cough in IPF is in the order of 30%. However, this reduction has not consistently been associated with patient reports of improvements in coughing, questioning the clinical benefit afforded. There is therefore a clear unmet need to help reduce cough and improve the quality of life for patients with IPF.

Opiates have long been advocated for the suppression of cough (13). Morphine is thought to depress the cough reflex, acting directly on the neural pathways in the brain. Antitussive effects occur with doses lower than those usually required for analgesia. In patients with refractory chronic cough 10mg of controlled release morphine sulfate every 12 hours, has been shown to cause significant suppression of cough, reducing objective cough frequency by

over 70% compared to placebo in clinical responders (13). While morphine is frequently used as a palliative agent for dyspnoea in IPF its effects on cough have never been tested (14). The aim of this project is therefore to explore the effect of low dose morphine, one of the few therapies shown to be effective in some patients with otherwise refractory chronic cough, in patients with IPF.

We hypothesise that compared with placebo, low dose (5mg) controlled release Morphine sulfate (MST) will reduce the number of coughs recorded during a 24hr period in patients with IPF.

We therefore aim to evaluate the within subject differences in objective cough frequency with morphine compared to placebo therapy in IPF. This Proof of Concept study will provide justification for and facilitate the planning of future studies to definitively assess the effect of morphine in IPF patients.

4.2 Investigational Medicinal Product (IMP)

The study IMPs are:

- controlled release encapsulated Morphine sulfate (MST) 5mg tablets and
- matched placebo taken orally twice daily as outlined in Section 14 of the study protocol.

4.3 Pre-clinical data

Opioids are commonly used for pain relief at higher doses than for cough and breathlessness. Whilst there are some studies detailing the effects of morphine on breathlessness in the context of chronic respiratory conditions, there are only a handful studying its effects in interstitial lung disease. A review by Kohberg *et al.* (14) included studies of morphine effects on dyspnoea in both COPD and IPF patients due to the lack of specific studies in IPF. Moreover, a total of only 18 IPF patients were included in the studies combined. Studies included oral, nebulised, subcutaneous and intravenous modes of administration. Nebulised morphine was found to be ineffective (5 out of 7 studies). This may be explained by the mechanism of dyspnoea originating from a central drive in such patients. The authors commented that whilst some patient reported symptomatic benefit was observed in the studies combining COPD with IPF patients, the effects were inconclusive.

Allen and colleagues published a non-randomized study in IPF-specific patients (15) which evaluated the effect of diamorphine, administered subcutaneously followed by oral morphine (most patients required less than 20mg daily) with a significant improvement in dyspnoea score. There was also no significant drop in systolic blood pressure or oxygen saturation with subcutaneous diamorphine. However, this was a very frail group with 11 end-stage IPF subjects, with mean survival of 5 weeks after commencing opioids.

The effects of nebulised morphine specifically in patients with interstitial lung disease has been evaluated in a small randomized double-blinded placebo controlled study where 3 out of 6 patients had a diagnosis of IPF (16). While the authors concluded that there was no

improvement in dyspnoea or exercise tolerance, only small doses were administered (2.5 to 5mg).

A more recent retrospective study focussed on palliative symptom control of intravenous morphine infusions in 22 patients (13 with IPF) with acute exacerbation of advanced interstitial lung disease (17). The majority (21/22) of the patients required more than 10 Litres/min of oxygen therapy, with 10 patients having peripheral oxygen saturations of less than 85% despite supplemental oxygen. The starting dose was 5 to 10mg in a 24-hour period, and this provided relief of dyspnoea in 77% of patients. However, half of the patients required further midazolam to treat breathlessness in the terminal phases of their lives. It is obvious that conducting randomized trials in such severely impaired patients is unethical, hence the lack of studies in this field.

The only randomised control trial evaluating opioids in chronic cough was conducted by Morice and colleagues (13) in 27 patients, where a starting dose of 5mg twice daily slow release morphine (MST) was shown to be effective in reducing diary recorded cough scores. The study ran an open label extension period, allowing patients to increase the dose of MST to 10mg twice daily according to patient choice. Interestingly, there was no significant difference in cough severity or Leicester Cough Questionnaire (LCQ) score between those that took 5mg and 10mg twice daily. Furthermore, despite the side effects of constipation and drowsiness, all patients completed the study. This highlights the tolerability of low dose MST.

A large longitudinal cohort study in Sweden with over 1600 oxygen-dependent ILD patients revealed that opiates were used in 15% of patients and was not associated with either increased mortality or hospitalisation (18). This was true for both low and high dose (equivalent of 30mg daily oral morphine or higher) therapy. As for benzodiazepines, the study found increased mortality with high doses, but low doses were safe (18). This study confirms the safety of opioids in ILD patients, even in those who have more severe disease.

4.4 Clinical data

The PAciFy-Cough trial will be the first randomised control trial evaluating the effect of opioids on cough in IPF patients.

Our rationale for low dose morphine for the treatment of cough in IPF is to balance the effect of higher doses risking side effects, in particular nausea, constipation and drowsiness. These will all likely impact on the quality of life of patients. In addition, cough is a mechanism of expelling sputum, and is helpful in clearing chest infections, which are often triggers for acute exacerbations of IPF. High doses of opiates may impair this protective mechanism.

Our study design considers the previously mentioned single randomised control trial of MST in chronic cough (13). The investigators identified that those grouped as responders to morphine had benefited by Day 5 of treatment. This response persisted through the four-week study period. As our trial is a proof of concept study, the treatment period of 14 days is justified. Furthermore, as the 10mg twice daily dose did not improve cough severity or improve LCQ scores and resulted in more side effects, we concluded that our study should use the

5mg twice daily dosage in the treatment arm. The aim is to generate a complete dataset on 40 patients, which will be powered to detect difference in 24 hr cough frequency.

4.5 Study Rationale and risk/benefit analysis

Cough in IPF remains one of the most challenging symptoms to address. There are currently no licenced therapies and current clinical practice simply draws upon experience of cough in other diseases. To date there have been very limited trials targeting cough in IPF. Thalidomide has been shown to be beneficial in a randomised control trial, however it's side effects profile renders it practically useless (10). Pirfenidone, has shown some promise in a recent trial (19) as has a nebulised form of sodium cromoglicate (12). None of these therapies have to date been able to demonstrate a clinically meaningful improvement in cough or quality of life for patients with IPF.

Morphine is thought to have centrally acting suppression on the cough reflex. Antitussive effects occur with doses lower than those usually required for analgesia (13). This study is a proof of concept study using MST and the dose that will be used in this study is low (5mg twice daily). This will minimise the exposure to side effects and we anticipate that this dose of MST will be well tolerated. Indeed, in current clinical practice MST is used in IPF in the context of palliative symptomatic control of breathlessness and is safe and well tolerated. We will exclude patients under the age of 18 years, and pregnant females.

We anticipate that this study will demonstrate the beneficial effect of morphine on cough in patients with IPF, and if this is the case may provide direct benefit to the subjects for taking part in the study.

4.6 Management of potential study risks

The usual dose of MST in patients with moderate to severe pain is 30mg every 12 hours. At this dose, the commonest side effects are nausea, vomiting, constipation and drowsiness. With chronic therapy, nausea and vomiting are unusual with MST controlled release tablets, but should they occur the tablets can be readily combined with an anti-emetic if required. Constipation may be treated with appropriate laxatives.

The dose (5mg) that patients will take in this study is significantly lower than that required for pain. Therefore, we do not expect any significant side effects in addition to those listed above. In a randomised controlled trial of MST in patients with chronic cough the commonest side effects were constipation (40%) and drowsiness (25%).

5 Study objectives

5.1 Primary objective

To demonstrate that Morphine Sulfate reduces cough frequency in patients with IPF compared to placebo. This will be measured using objective cough frequency at 14 days.

5.2 Secondary objectives

i) To evaluate the within subject differences in self-reported and objective cough frequency with morphine compared with placebo therapy.
ii) To explore the relationships between quality of life, anxiety, dyspnoea and the response to morphine.
iii) To explore the relationship between activity and cough and the response to morphine.
iv) To evaluate a range of exploratory biomarkers for cough and response to Morphine Sulfate.

6 Trial design

6.1 Overall design

A randomised, double blind, placebo controlled, two-way crossover, multicentre study to assess the physiological effect of controlled release Morphine Sulfate (MST) on the urge to cough and objective cough counts in subjects with idiopathic pulmonary fibrosis (IPF) (Figure 1).

The study will recruit 44 patients with a multidisciplinary diagnosis of IPF, over a 12-month period, across three interstitial lung disease units. Patients with IPF will be asked to attend the department for a total of 6 visits. Up to 44 patients with a diagnosis of IPF and self-reported troublesome cough will be recruited to generate a complete dataset on 40 patients. Patients will be randomised (1:1) to either placebo twice daily or MST 5mg twice daily for 14 days. Patients will then crossover after a 7 day wash out period. Those that were randomised to placebo will be given MST 5mg twice daily and those that were randomised to MST will take placebo for 14 days.

6.2 Dosage regimen and rationale

Morphine is thought to depress the cough reflex by direct effect on the cough centre in the brain. Antitussive effects occur with doses lower than those usually required for analgesia. In this study, patients will take 5mg of MST every 12 hours. This dose has been shown to cause significant suppression of cough in patients with refractory chronic cough [13]. Indeed, in the study by Morice and colleagues, an increased dose of MST from 5mg to 10mg twice a day resulted in increased drowsiness, without a significant improvement in reported cough severity.

6.3 Concomitant treatment

Patients will be permitted to use laxatives for side effect of constipation, and anti-emetics for nausea. The use of these medications will be documented in the clinical notes. Patients will be permitted to take concomitant anti-tussive medications and inhalers if they have been on a stable dose at least 4 weeks prior to the screening visit. Dose titrations of these medications

will not be permitted. Patients will not be permitted to take additional opiates (on top of MST or placebo), including on an as required basis (*e.g.* oramorph).

6.4 Prohibited concomitant medication

Between Day 0 and Day 35, patients will not be permitted to receive **additional opiates** (*e.g.* oramorph) * or to use **ACE inhibitors.**

* opiates within 14 days of the screening visit are also prohibited.

6.5 Schematic of trial design

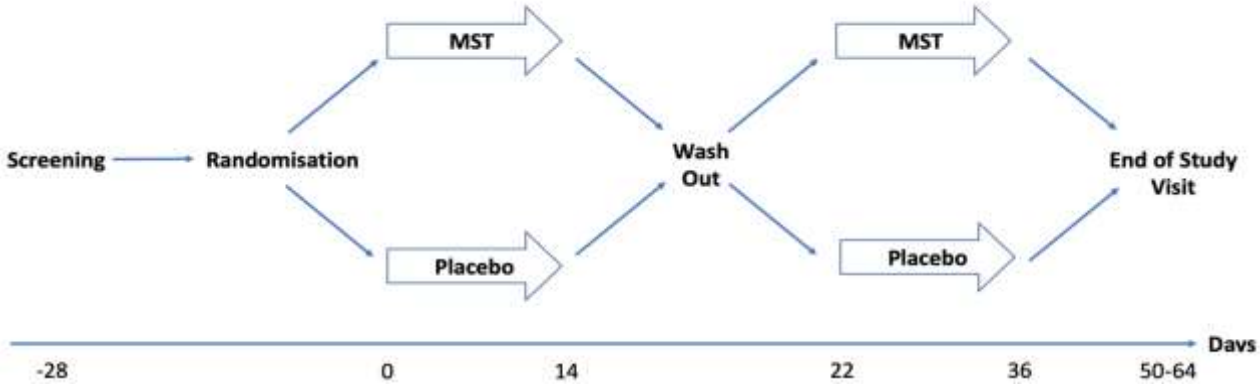

Figure 1: A randomised, double blind, placebo controlled, two-way crossover study investigating the effect of MST on cough in IPF.

7 Eligibility criteria

7.1 Inclusion criteria

1. Self-reported cough (> 8 weeks) with cough VAS ≥ 30/100
2. A diagnosis of IPF within 5 years prior to the screening visit, as per applicable ATS/ERS/JRS/ALAT guidelines, in line with hospital records
3. **Age**
   3.1 Male and female participants aged ≥ 40 – 90 years at the time of signing informed consent
4. **Sex:**
   4.1 **Male participants**: A male participant must agree to use contraception as detailed in Appendix 2 of this protocol during the study and for at least 90 days after the follow-up visit, and refrain from donating sperm during this period
   4.2 **Female participants**: A female participant is eligible to participate if she is not pregnant, not breastfeeding, and not a woman of childbearing potential (WOCBP) as defined in Appendix 2.
5. Meeting all of the following criteria during the screening period: FVC ≥ 45% predicted of normal, Forced expiratory volume in 1 second (FEV1)/FVC ≥0.7, DLCO corrected

for Hb ≥30% predicted of normal. Lung function performed within 12 months of the screening period is acceptable.
6. The extent of fibrotic changes is greater than the extent of emphysema on the most recent HRCT scan (investigator determined within 24 months of the study screening visit).
7. Written informed consent.

7.2 Exclusion criteria

1. Treatment with immunosuppressive therapy or antibiotics within last 4 weeks of screening visit. A stable dose of corticosteroids equivalent to prednisolone of 10 mg per day or less, if used for an indication other than pulmonary disease will be permitted.
2. Current smoker
3. History of alcohol and drug(s) addiction
4. Regular use of sedative therapies
5. Acute IPF exacerbation within 6 months prior to screening and/or during the screening period.
6. Concurrent use of pirfenidone or Nintedanib, unless receiving a stable dose for at least 8 weeks prior to screening
7. Use of ACE inhibitors
8. Patients with co-existent conditions known to be associated with the development of fibrotic lung disease. This includes; connective tissue disease, suspected drug-induced lung disease, asbestosis or other asbestos related disease (pleural plaques, mesothelioma), granulomatous disease including sarcoidosis. Patients with an auto-immune profile considered diagnostic for a specific connective tissue disease will be excluded, even in the absence of systemic symptoms. Non-specific rises in auto antibodies *e.g.* rheumatoid factor, anti-nuclear antibody etc. will not be used to exclude individuals from the study.
9. Significant other organ co-morbidity including hepatic or renal impairment and pulmonary hypertension (investigator determined).
10. Significant coronary artery disease (myocardial infarction within 6 months or ongoing unstable angina within 4 weeks of screening visit) or congestive cardiac failure based on clinical examination
11. Patients at significant risk for side effects, intolerance or allergy to morphine
12. Pregnant and breastfeeding patients, or women of child-bearing potential, not using a reliable contraceptive method (see Appendix 2). A urine pregnancy test will be performed in females of child-bearing potential at the initial study visit.
13. Unable to provide informed written consent
14. Predicted life expectancy < 6 months
15. Use of long-term oxygen therapy. Use of ambulatory oxygen will be permitted.
16. Current or use of opiates within 14 days of the screening visit.

8 Subject/Patient Recruitment process

Individuals who meet a multi-disciplinary diagnosis of IPF based on established international criteria will be recruited prospectively from the Royal Brompton Hospital, Manchester University NHS Foundation Trust (MFT) and Aintree University Hospital NHS Foundation Trust. We will include subjects with a cough VAS score of 30 or over, in line with other clinical studies. It's plausible that some drugs work equally in all cough frequencies or even better in less severe cough frequency, and pre-screening would fail to capture this.

Patients with an established diagnosis of IPF will be approached at clinic, the study will be explained, and a participant information sheet (PIS) will be given to interested parties. Patients will also be identified from an existing database and an invitation letter and information sheet describing the study will be sent by post. This will be followed by a telephone conversation a minimum of 24 hours later to establish interest and answer any questions before booking in for visit 1. Patients will be provided with a full explanation of the study at visit 1 and be given the opportunity to ask questions before providing written consent.

Patient recruitment at a site will only commence once the trial team has ensured that the following approval/essential documents are in place:

1. The main REC, and Clinical Trial Authorization (CTA) approval,

2. Final sponsorship and/or confirmation of Capacity and Capability (previously known as NHS Permission),

3. Sponsor has conducted the trial initiation procedure

4. Local Site Delegation of Duties and Signature Log is completed.

All sites participating in the trial will also be asked to provide a copy of the following:

1. Signed Clinical Trial Site Agreement (CTSA),

2. Confirmation of Capacity and Capability (previously known as NHS Permission)

3. Signed Delegation of Duties and Responsibilities Log.

9 Study procedures

9.1 Informed consent

Informed consent will be obtained by the Chief Investigator (CI), Principal Investigator (PI) and/or a nominated deputy as recorded on Sponsor's Delegation of Responsibilities Log. Only those members of the study team who have clinical responsibility for the care of patients under the care of the general medical service will be permitted to undertake informed consent. All individuals taking informed consent will have received training in Good Clinical Practice (GCP).

Consent to enter this study will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the patient has had the opportunity to deliberate. The patient will be allowed to specify the time they wish to spend deliberating, usually up to 24 hours.

Periods shorter than 24 hours will be permitted if the patient feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the patient has fully retained, understood and deliberated on the information given. This provision has been made with the support of our patient advisory group.

Likewise, periods longer than 24 hours will be permitted should the patient request this. The Investigator or designee will explain that the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site (one filed in the medical notes and one field in the TMF). A copy of the consent form will also be given to the patient.

If new safety information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

9.2 Randomisation procedure

Subjects will be randomised sequentially to a sequence group defining the order in which active drug and placebo are given, according to a computer-generated schedule (Sealed Envelope EDC). Access to the database at each participating centre will be restricted to authorised study staff.

All patients will be given a study specific 24hrs emergency contact card immediately after being randomized. The card includes details of the study: Study title, details of IMP(s), patient trial number, CI/PI's contact details along with out of hours contact details in case of emergency.

9.3 Emergency unblinding

This will be a double-blind study with both the patient and investigator blinded to study treatment. The investigator or treating physician may un-blind a patient's treatment assignment in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the patient. The investigator will make the decision to un-blind and have 24-hour access to un-blinding the treatment assignment *via* the electronic database system (Sealed Envelope EDC).

If the Sealed Envelope EDC system is not accessible for technical reasons (*e.g.* electronic failure of the database), a manual back up system is also available. A master randomization

list will be provided to the Sponsor (RB&HFT) pharmacy department. If the Sealed Envelope EDC system is not accessible for technical reasons, then the investigator will contact RB&HFT hospital pharmacist (and/or an on-call pharmacist outside of working hours) *via* RB&HFT switchboard (Phone: 0207 352 8121) for the manual un-blinding of the treatment assignment. The investigator must notify the Sponsor as soon as possible. The date and reason for the un-blinding must be recorded in the appropriate data collection tool, eCRF.

A patient will be withdrawn if their treatment code is un-blinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the un-blinding) will be recorded in the eCRF.

10 Study Assessments

Patients will be asked to attend the department for study visits on 3 occasions. In addition to three (3) hospital visits, the research team will conduct two (2) remote study visits to ensure safety of the study patients for the duration of the study.

A summary of study visits and procedures is shown in Appendix 1.

10.1 Pre-Screening (day -28 to day -1)

The pre-screening phase (minimum of 1 day, maximum of 28 days where necessary) is designed to establish baseline characteristics.

Patients with ILD, who are potentially eligible to commence study treatment, will initially be identified by members of their clinical care team, *via* pre-screening of medical records. The research teams will send a copy of the pre-screening study letter and the study PIS with contact details, to enable potentially eligible study participants to contact the research team, if interested to take part. This will be followed up by a telephone call to obtain provisional verbal consent and review eligibility criteria in more detail to prevent any unnecessary travel.

Verbal consent obtained over the phone will be clearly documented in patients' medical records and the CRF.

10.2 Visit 1 - Baseline Screening and Randomization Visit (Day 0)

The screening and baseline visit will be conducted on the same day. This visit is designed to confirm eligibility and establish baseline characteristics. The investigator or designee will review the inclusion and exclusion criteria with the patient to confirm eligibility.

If all inclusion and exclusion criteria are met at the end of the screening phase the patient will be randomised as described in Section 9.2 of the study protocol. All randomized patients will undertake baseline investigations in the order outlined below and in the Schedule of Events prior to initiation of therapy. *For women of childbearing potential with a negative pregnancy test (see Appendix 2) there will be a maximum of 7 days between screening and first dose of IMP.*

At the screening baseline visit the following assessments will be undertaken:

- Written informed consent
- Assessment of inclusion/exclusion criteria
- Demographics, medical history
- Concomitant medication review
- Physical examination
- Vital signs to include measurements of body temperature, heart rate, blood pressure, O_2 saturation and respiratory rate.
- Routine blood tests (full blood count, renal and liver function)
- Collection of blood for RNA, DNA and Biomarker analysis
- Quality of Life Questionnaires
- Pregnancy test for women of childbearing potential (WOCBP) as defined in Appendix 2. Those subjects, that are not pregnant and are eligible to participate in the study, they must commence study treatment within seven (7) days of the screening visit. Where this is not possible, a pregnancy test must be scheduled within seven (7) days of fist dose of IMP.
- Spirometry and gas transfer (if lung function test is available from within the last 12 months, this is not required.
- Attach 24hrs ambulatory cough monitor and Fitbit and provide pre-paid envelope for return of both
- Randomization
- IMP dispensing.

10.3 VISIT 1a – Telephone Call (24hrs post Visit 1, Day 1)

- At the end of the 24-hour cough monitoring period on day 1, a researcher will telephone the patient to instruct them to remove the monitor then start taking their prescribed study medicine the day after the visit (Day 1).
- The cough monitor and Fitbit are to be returned to the researcher *via* a pre-paid envelope.

- During a telephone call, all study patients will be reminded of a requirement to retain any unused IMP for IMP reconciliation at the next study visit, which will be conducted remotely.

- Researcher will post out a new cough monitor and Fitbit with a pre-paid envelope (in time for visit 2).

10.4 Visit 2 – 1st Follow up visit (Day 14) – Remote visit

The investigator or designee will conduct this visit remotely *via* a suitable smartphone platform (*e.g.* Zoom) to undertake the necessary clinical and study procedures in the order outlined in the Schedule of Events. These include:

- AE review

- Review of concomitant medication

- Global Impression of Change

- Quality of Life Questionnaires

- Patient to attach 24hrs ambulatory cough monitor and Fitbit monitor themselves, assistance to be provided *via* a suitable smartphone platform.

- IMP reconciliation/accountability. A member of the research team will count the number of doses that were unused and record in the CRF. The patient will be reminded to retain all unused doses of IMP and bring them to the next hospital visit (Visit 3).

10.5 VISIT 2a – Phone call (24hrs post Visit 2, Day 15)

- At the end of the 24-hour cough monitoring period following Visit 2, a researcher will telephone the patient to instruct them to remove the cough monitor and Fitbit.

- The cough monitor and Fitbit will be returned to the researcher *via* a pre-paid envelope.

- Patients will be reminded to bring all unused IMP to the next hospital visit (Visit 3).

During visit 2a, all study patients will be reminded of a washout period of 7 days.

10.6 Visit 3 – Crossover visit (Day 22)

After a 7 day wash out period all study patients will return to cross over between Morphine Sulfate and placebo depending on the initial medicine prescribed at Visit 1. The investigator or designee will review the patient and will undertake the necessary clinical and study procedures in the order outlined in the Schedule of Events. These include:

- Vital signs to include measurements of body temperature, heart rate, blood pressure, O_2 saturation and respiratory rate.

- AE review

- Review of concomitant medication

- Quality of Life Questionnaires

- Attach 24hrs ambulatory cough monitor and Fitbit and provide pre-paid envelope for return of both.

- IMP dispensing

- Collect unused IMP and return to pharmacy for reconciliation.

10.7 VISIT 3a – Phone call (24hrs post Visit 3, Day 23)

- At the end of the 24-hour cough monitoring period following Visit 3, a researcher will telephone the patient to instruct them to remove the monitor then start taking their prescribed study medicine the day after the visit (Day 23).

- The cough monitor and Fitbit will be returned to the researcher *via* a pre-paid envelope.

- During a telephone call, all study patients will be reminded of a requirement to return the study IMP at the next hospital study visit (Visit 4).

10.8 Visit 4 – Crossover Follow up visit (Day 36)

The investigator or designee will review the patient and will undertake the necessary clinical and study procedures in the order outlined in the Schedule of Events. These include;

- Vital signs to include measurements of body temperature, heart rate, blood pressure, O_2 saturation and respiratory rate.

- AE review

- Review of concomitant medication

- Global Impression of Change

- Quality of Life Questionnaires

- Attach 24hrs ambulatory cough monitor and Fitbit and provide pre-paid envelope for return of both.
- Pregnancy test (for WOCBP as described in Appendix 2)
- IMP reconciliation/accountability.

10.9 VISIT 4a – Phone call (24hrs post Visit 4)

- At the end of the 24-hour cough monitoring period following Visit 4, a researcher will telephone the patient to instruct them to remove the monitor.
- The cough monitor and Fitbit will be returned to the researcher *via* a pre-paid envelope.
- All study patients will be reminded to return any unused study IMP, along with packaging, for IMP reconciliation (if it has not been completed during visit 4).

10.10 VISIT 5 – End of Study Visit (Day 50-64) – REMOTE VISIT

- AE review over the phone.

10.11 Unscheduled Visits

Patients may require an unscheduled visit in addition to the regular scheduled protocol visits (*e.g.* symptoms of infection, worsening of disease, or assessment of AEs). If a patient requires an unscheduled visit, the study centre will be strongly encouraged to undertake the following assessments:

- Physical examination
- Vital signs to include measurements of body temperature, heart rate, blood pressure, O_2 saturation and respiratory rate.
- AE review
- Concomitant medication review
- Lung function (spirometry and gas transfer)
- Collection of blood for laboratory analyses (to include full blood count, ESR, urea and electrolytes and liver function tests)
- ECG (optional).

10.12 Summary flow chart of study assessments

Please see Appendix 1 of the study protocol.

11 Methods

11.1 Laboratory procedures

Routine safety blood tests including full blood count, U&E's and liver function tests will be undertaken in the clinical laboratories at local sites according to local policies and procedures. Copies of local reference ranges will be collected.

11.2 Quality of Life, Cough and Breathlessness Assessment

Quality of life, self-reported cough and breathlessness will be assessed by self-administered questionnaires (adapted to the language and culture of each country). These are completed at baseline and repeated at all follow up visits and the end of study visit.

The instruments used will be the Leicester Cough Questionnaire, Cough severity VAS, Dyspnoea-12 (D-12), the L-IPF, Kings Brief ILD and the Hospital Anxiety and Depression Scale (HADS) questionnaire. A global impression of change in quality of life, cough and breathlessness will also be recorded.

11.3 Efficacy Assessments

Measurement of cough frequency will be done using objective digital cough monitoring. The digital cough monitor consists of a portable sound recording device, which is worn in a pouch or pocket. The small microphone is clipped onto the subject's collar or lapel, as close as possible to the anterior neck. A continuous sound recording is made for up to 24 hours. The digital recording is then processed through accompanying computer software, which automatically registers sound patterns typical for cough. Software output provides the total number of cough events over the entire time period of recording and average hourly cough frequency.

11.4 Research Blood Samples

All biological samples for future research will be collected and handled according to a study specific procedure, stored anonymously and labelled using a unique study number to permit accurate linkage to clinical data. Samples will be initially processed and stored at study sites in accordance with the study specific procedure for handling PAciFy Cough biological samples, to facilitate transfer to the Royal Brompton Hospital (RBH) Biological Research Unit (BRU) Royal Brompton Hospital (RBH), Sydney Street, London, SW3 6NP.

The exploratory analysis of potential serum biomarkers and blood transcriptomics may be undertaken at; the Royal Brompton Hospital (RBH), Imperial College London, a commercial research organization (CRO) or in collaborating academic institutions. Analysis of these samples may be undertaken after completion of the study and following assessment of the primary study outcome.

The storage of samples and use in future unspecified research will be performed in accordance with the Human Tissue Act 2004, and the RBH policy for 'the acquisition, storage and use of Human biological specimens for research'. Stored samples may be used to assess future biomarkers for the risk of developing lung fibrosis and the prognosis of this condition.

We will ensure that participants are aware of this and details will be included in the Patient Information Sheet (PIS) and the consent form.

12 Definition of the End of Trial

The end of trial is defined as the last patient last visit (LPLV).

13 Discontinuation/withdrawal of participants and stopping rules

Patients may decide to withdraw early from the study, or the research physician may feel that it is in the best interests of the patient to terminate their involvement in the study prior to completion for safety reasons. Patients who wish to withdraw their consent do not have to give a reason to do so. Early withdrawal will be clearly documented in the case report form (CRF) and the hospital case notes. All unused medications will be returned.

Patients will be withdrawn from the study if they develop a condition that would compromise their safety, and the decision is made by an Investigator. Patients who withdraw from the study will not be replaced.

If the Sponsor decides to terminate the study, the patients will be informed and the reason for termination will be documented in the CRF.

14 IMPs and non-IMPs used in the trial

14.1 Name and description of each IMP

a) The IMP is an over-encapsulated **Morphine Sulfate** prolonged release 5mg tablet (MST®CONTINUS®), Napp Pharmaceuticals Limited, PL 16950/0035 (MST® CONTINUS®).

b) The **placebo** is a DBAA capsule containing Microcrystalline Cellulose Ph. Eur.

14.2 Source of IMPs including placebo

Manufacturing, packaging and labeling of the over-encapsulated Morphine Sulfate prolonged release 5mg tablets and matched placebo tablets will be carried out by:

Royal Free Pharmaceutical Production Unit

Pond Street, Hampstead

NW3 2QG

London, UK

It is expected that approximately 1,800 capsules of the active and placebo, will be manufactured over two campaigns. The MST and placebo capsules will be visually inspected and packed into Plastic White HDPE Screw Neck Bottle - 200 ml with Tamper Evident and Child Resistant cap.

The Sponsor has contracted The Royal Free Pharmaceutical Production Unit to undertaken packaging, labelling and QP release of study IMPs in compliance with Good Manufacturing Practice (GMP) and Annex 13. Accountability procedures for the IMP(s).

The local pharmacy hospital department at each study site will be responsible for maintaining & updating the IMP Accountability Log during the cross-over treatment period of the study (Visits 3 and 5), filed in the hospital pharmacy file. The local pharmacy hospital department at each site will also be responsible for record keeping as per Controlled Drug regulations in accordance with local practice.

IMP(s) destruction will be conducted, once agreed by the Sponsor, in accordance to local pharmacy practice and Controlled Drugs regulations in accordance with local practice. It will be documented on the IMP Destruction Log in the hospital pharmacy file.

All unused IMP(s) that are dispensed should be returned to the trial pharmacist for accountability purposes.

14.3 Route of administration, dosage, dosage regimen, and treatment period(s) of the IMPs

Patients will be randomized to receive placebo or Morphine Sulfate prolonged release for the first study period (14 days at Visit 2 and cross-over treatment for 14 days at Visit 4).

The patients will be instructed to take one capsule (placebo or morphine sulfate prolonged release 5 mg) orally twice daily according to the prescribed dosing schedule.

14.4 Dosage modifications

There will be a fixed dose of MST 5mg twice daily, and there will be no dosage adjustments.

14.5 Assessment of compliance

The researcher will check patients' compliance at the end of each treatment period. To assess compliance, the number of tablets returned to the hospital pharmacy will be compared to the number distributed and assigned dose level.

14.6 Post-trial IMP arrangements

Patients will be assessed on a case by case basis across all participating sites and will be given an option to remain on the study drug if there appears to be a benefit to them.

14.7 Name and description of each non-IMP (NIMP)

No nIMPS will be administered as part of the trial.

15 Pharmacovigilance

15.1 Definitions

Adverse Event (AE)—any untoward medical occurrence in a patient or clinical trial subject who is administered an IMP and which does not necessarily have a causal relationship with this treatment. (i.e. any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom an IMP has been administered, including occurrences unrelated to that product)

Adverse Reaction (AR)—any untoward and unintended responses to an IMP related to any dose administered. (i.e. any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom an IMP has been administered and related to any dose administered)

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)—any Adverse Event or Reaction in a trial subject that:

- Results in death; or
- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the IMP regardless of time of diagnosis).

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR)—an Adverse Reaction which is classed in nature as both serious and unexpected.

An Unexpected Adverse Reaction is an Adverse Reaction, when both the nature and severity of the event is not consistent with the information about the medicinal product in question, as set out below:

(a) in the case of a product with a marketing authorization, in the Summary of Product Characteristics (SmPC) for that product,
(b) in the case of any other IMP, in the Investigator's Brochure relating to the trial in question.

15.2 Terminology for classification of AEs

A simple and brief description of **clinical symptoms** should be given using the following descriptions to record information about AEs:

1. Severity will be described using the following categories:

- **Mild**—the adverse event does not interfere with the volunteer's daily routine and does not require intervention; it causes slight discomfort.
- **Moderate**—the adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort.
- **Severe**—the adverse event results in alteration, discomfort or disability which is clearly damaging to health.

2. Relationship to treatment — the assessment of relationship of AEs to the administration of IMP is a clinical decision based on all available information at the time of the completion of the CRF. The following categories will be used:

- **Definitely**—there is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably**—there is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly**—there is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (i.e. the patient's clinical condition, other concomitant events).
- **Unlikely**—there is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
- **Not related**—there is no evidence of any causal relationship.
- **Not Assessable**

3. Expectedness will be described using following categories:

- **Expected**—an AE which is consistent with the information about the IMP listed in the Reference Safety Information (RSI), in Section 4.8 of the SmPC of morphine sulfate (or the Investigator Brochure).
- **Unexpected**—an AE which is not consistent with the information about the IMP listed in the Reference Safety Information (RSI), Section 4.8 of the SmPC of morphine sulfate (or the Investigator Brochure).

15.3 Recording of Safety Information

Collection, recording and reporting of AEs (including serious and non-serious events and *reactions) to the Sponsor will be done according to the Sponsor's Pharmacovigilance SOP.*

15.3.1 Adverse Events (AEs)

All Adverse Events will be recorded in the hospital notes in the first instance.

A record of all AEs, whether related or unrelated to the treatment will also be kept in the CRF.

If the Investigator suspects that the disease has progressed faster due to the administration of the IMP, then he will report this as an unexpected adverse event to the sponsor.

15.3.2 Serious Adverse Events (SAEs)

All SAEs will be recorded in the hospital notes and the CRF, and the Sponsor's SAE Recording Log. The SAE Log will be sent to Sponsor on request and every 2 months.

All SAEs will be reported to the Sponsor *via* the Research Office (RO) dedicated mailbox on an SAE form unless otherwise stated in the protocol. The Chief or Principal Investigator will complete the Sponsor's SAE form and the form will be faxed to the RO on 020 351 8578 or E-mailed to safetyreporting@rbht.nhs.uk, within 24hrs of the Investigator becoming aware of the event.

The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible.

15.3.3 Expected SAE/Rs Related to IMP

Expected Adverse Reactions are those which are specified in Section 4.8 'Undesirable Effects' of the SmPC of morphine sulfate.

15.3.4 Expected SAEs Related to Underlying Disease

Events that do no requires expedited reporting for this study are those which are expected and related to underlying disease, which include study endpoints and disease progression or worsening of pre-existing respiratory symptoms, unless the investigator judges the event as related to use of the IMP.

15.3.5 SUSARs

Investigators must complete the appropriate SAE form on the eCRF and an automatic email notification will be sent to the Trial Manager, CI and Sponsor. The Trial Manager will ensure the SUSAR report is un-blinded and is reviewed by the CI or designee within 2 days and adjudicate whether the event constitutes a SUSAR.

The Trial Manager will ensure that fatal or life threatening SUSARs are reported to the MHRA and the main REC as soon as possible, but no later than 7 calendar days after the receipt of the eSAE report. Any additional information will be reported within 8 days of sending the first report. The Trial Manager must report all other SUSARs and safety issues to the MHRA and main REC, as soon as possible but no later than 15 calendar days after the Sponsor has first knowledge of the minimum criteria for expediting reporting.

15.4 Notification of deaths

All deaths will be reported to the Sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event.

15.5 Reporting to Regulatory Authority

The RO will notify all SUSARs to the MHRA electronically *via* e-SUSARs Database and the main REC using the CIOMS form. The CIOMS form should be completed by the CI and PI at each site and sent to the RO along with the Sponsor's SAE Recording and Reporting Form as described Section 12.2 of the protocol.

The RO will inform the MHRA and the main REC of fatal or life threatening SUSARs as soon as possible, but no later than 7 calendar days after the RO receives the SAE report form. Any additional information will be reported within 8 days of sending the first report.

The RO must report all other SUSARs and safety issues to the MHRA and main REC, as soon as possible but no later than 15 calendar days after the RO has first knowledge of the minimum criteria for expediting reporting.

15.6 The type and duration of the follow-up of subjects after AEs

Any SUSAR related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred. Any adverse events occurring up to and including the final study visit will be recorded. Follow up and care for patients suffering an Adverse Drug Reaction (ADR) will be provided as required by clinical need.

All SAEs will be followed up every two weeks until resolution.

15.7 Development Safety Update Reports

The CI or a delegated PI will prepare the DSUR, using the Sponsor's DSUR template and in accordance with the Sponsor's DSUR SOP. It will be reviewed by the Sponsor and when necessary be referred to an independent committee (*i.e.* Clinical Trials Oversight Committee (CTOC)). The RO will provide the main REC and the MHRA with a copy of the study DSUR.

15.8 Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR. It will be reviewed by the JRO and sent to the main REC within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, and annually until the trial is declared ended.

15.9 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until the follow-up visit. All women of childbearing potential (WOCBP) will be asked to undertake a pregnancy test at the screening study visit, and a maximum of seven (7) days is permitted from the test date and the first dose of the IMP. Those patients that are pregnant will be excluded from the study.

In the event of a pregnancy during the study:

- The Investigator should inform the Sponsor within 24 hours of learning of the pregnancy
- all pregnancies will be recorded in the source data file and the Pregnancy Reporting Form in the eCRF
- The Investigator should continue to follow up the procedures outlined in Appendix 2 of the protocol.

Patients who become pregnant during the study will be excluded from further administration of IMP but will continue to be followed up in study visits.

Abnormal pregnancy outcomes (*e.g.* spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

15.10 Reporting Urgent Safety Measures

Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928 states "the Sponsor and the Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. If measures are taken, the Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures."

In order to prevent any delays in the reporting timelines the Sponsor has delegated this responsibility to the CI/PI. Therefore, the CI/PI must report any urgent safety measures to the MHRA directly, and in parallel to the Sponsor.

Please refer to the following website for details on clinical trials safety reporting: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

15.11 Notification of Serious Breaches of GCP and/or the protocol

Any Protocol Deviations, Violations, Potential Serious Breaches and Urgent Safety Measures will be recorded using the Sponsor's Log issued during the Sponsor's Trial/Site Initiation meeting/visit.

Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument2006/1928, contains a requirement for the notification of "serious breaches" of GCP or the trial protocol:

(1) The Sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of:

(a) The conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

(2) For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the subjects of the trial; or

(b) The scientific value of the trial.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The Sponsor's SOP on the Protocol Violation/Deviations and Serious Breaches will be followed.

16 Data management and quality assurance

16.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 2018.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, Date of Birth (DOB) and trial Identification Number (ID), will be used for identification.

16.2 Data collection tool

Case Report Forms (CRFs) will be designed by the CI and the final version will be approved by the Sponsor. All data will initially be entered legibly in black ink with a ball-point pen in the paper CRF (study worksheets). If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the paper CRFs. The Delegation of Responsibilities Log will identify all trial personnel responsible for data collection, entry, handling and managing the database. Paper CRFs will be considered source documents for this study.

Source documents are original documents and records from which participants' data are obtained. These also include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, correspondence and CRF entries themselves. A source document location log will be completed and filed in the investigator site file indicating what constitutes source data and where it will be located.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent form, the participant will be referred to by the study participant number, not by name.

Objective cough monitoring involves audio recordings to identify coughing. This involves wearing a small recording device which captures the cough sounds through two microphones and records them in a digital format. The recording is then processed through computer software to eliminate any segments where there is no voice activity. It is possible that despite this processing by the software, some of the subject's conversation is also captured in addition to their cough sounds. Prior to enrolment in the trial, this possibility would be explained to the subjects and outlined in the study Patient Information Sheet (PIS). Any conversation recorded in this manner would be treated with strict confidentiality.

16.3 Data handling and analysis

All data collected *via* paper CRFs will be transcribed to an electronic Case Report Form (eCRF) system. The Castor EDC system will be used to develop the eCRF and will be designed in accordance with the requirements of the clinical trial protocol and will comply with regulatory requirements. Local personnel will be trained on the Castor EDC system. Access will be restricted to site personnel, trial managers, trial monitors and the data management team. Personnel will have individual logon and passwords. It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the eCRFs. Trial monitors will check the accuracy of the eCRF data against source documents.

It is anticipated that the majority of source data (medical progress notes and letters, tests and investigations) will be filed in the individual patients' medical records. Any deviation from source data being present in the medical notes will be identified and documented. The eCRF and source documents must be available at all times for review by the Sponsor's clinical trial monitor, auditors and for inspection by the Medicines Health Regulatory Agency. The accuracy of eCRF data will be verified by review of the source documents and details will be provided in the trial Monitoring Report.

17 Archiving arrangements

The trial documents (including the Trial Master File (TMF), Case Report Forms (CRFs), Informed Consent Forms along with the trial database) will be kept for a minimum of five years. They will be stored in locked offices within the Royal Brompton Hospital site for the duration of the study. The Chief Investigator is responsible for the secure archiving of trial document. The trial database will also be kept electronically on the Trust computer network, for a minimum of five years.

The approved repository for longer retention of local materials for studies that involve RB&HFT patients is **Box-It Storage UK**. The study documentation will be prepared for archiving by the research team in line with the Research Office Archiving SOP and the transfer will be arranged by the Research Office.

18 Statistical design

18.1 Statistical input in trial design

The design and analysis plan of the trial has received formal statistical input form Prof Jacky Smith and Mr Winston Banya. The study is being undertaken in the UK sites only and all power calculations are based on UK sites only.

18.2 Endpoints

18.2.1 Primary endpoints

- The primary efficacy endpoint is the percent change in daytime cough frequency (coughs per hour) from baseline as assessed by objective digital cough monitoring at Day 14 of treatment.

18.2.2 Secondary endpoints

- Change from baseline in health-related quality of life scores (L-IPF, HADS, K-BILD)
- Change from baseline in self-reported cough (LCQ & VAS)
- Change from baseline in Dyspnoea (D12)
- Change from baseline in global impression of change in quality of life, cough and breathlessness.
- Proportion of responders with a minimum of 20% decrease from baseline at the end of treatment in 24-hour average cough count.

18.2.3 Exploratory endpoints

- Change in candidate serum biomarkers of fibrosis following therapy.

- Association of activity and cough frequency.

18.3 Sample size and recruitment

18.3.1 Sample size calculation

Based on previous repeatability data in IPF patients studied over a 11 day period a sample size of 40 subjects will have 90% power to detect a true difference in 24h cough frequency on the natural log scale -0.132 or 0.132 (equivalent to ~35% change) with a probability (power) of 0.9; assuming a within subject standard deviation of 0.310 (natural log scale) and the standard significance level of 0.05. Allowing for a 10% drop out rate, we will aim to recruit 44 patients for the study.

18.3.2 Planned recruitment rate

Subject to obtaining a favourable opinion from the Research Ethics Committee, we aim to start the study in March 2020 and to complete it by March 2022.

18.4 Statistical analysis plan

Summary statistics will be presented by treatment group. For continuous variables, unless otherwise stated, the number of available observations (n), mean, standard deviation, median, and range will be provided. For categorical variables, the number and percentage in each category will be displayed.

18.4.1 Primary endpoint analysis

The primary efficacy endpoint is the change from baseline in log-transformed 24-hour average cough count at the end of treatment. The primary analysis will be conducted using a linear mixed model for repeated measures (MMRM) adjusting for baseline measures and assessing any influence of treatment, centre, sequence or period. In the primary analysis model, all available data from each subject will be included.

18.4.2 Secondary endpoint analysis

Secondary efficacy endpoints will be summarized using descriptive statistics. For continuous endpoints (*e.g.,* change from baseline), summaries will include mean, median, standard deviation, minimum, and maximum. For discrete variables (*e.g.*, frequency), summaries will include number of instances and percentage of total instances for that category or time period. Quantitative secondary endpoints will be analysed using analysis of covariance (ANCOVA) models and proportion endpoints will be analysed using logistic regression models. All secondary analyses will be conducted using two-sided tests at the alpha=0.05 level of significance.

18.5 Interim analysis

No formal interim analysis is planned. A regular review of safety data will be conducted to monitor the safety of patients in the trial. A Data Monitoring Committee (DMC) will follow number of deaths, early discontinuation due to Adverse Events (AEs) and Serious Adverse Events (SAEs) in an un-blinded fashion. The first meeting will be held to review all available data after the 12th randomized patient has completed the last study visit and periodically thereafter. The complete details will be outlined in a DMC charter to be agreed by the DMC members at the start of the study.

19 Committees in involved in the trial

The study sponsor is Guy's and St Thomas' NHS Foundation Trust (GSTFT), Royal Brompton and Harefield Hospitals (RBHH). The Chief Investigator (CI) is Dr Philip Molyneux at the Royal Brompton Hospital (RBH).

An independent Trial Steering Committee (TSC) will be established to oversee the conduct of the study. It is anticipated that the TSC will comprise the lead investigators, an independent chair, two additional independent members, at least one of whom will be a patient/public representative. The TSC will develop terms of reference outlining their responsibilities and operational details. The TSC will meet before the trial commences and as required during the course of the study. Already recruited TSC members have participated in clinical trial design and have provided data to guide feasibility and safety.

20 Direct access to source data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

21 Ethics and regulatory requirements

The Sponsor will ensure that the trial protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and submitted supporting documents have been approved by the MHRA and a main Research Ethics Committee (REC), prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before site(s) can enrol patients into the trial, the Principal Investigator must apply for Site Specific Assessment from the Trust Research & Development (R&D) and be granted written NHS R&D approval. It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 12 for details of reporting procedures/requirements).

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply a summary report of the clinical trial to the MHRA and main REC within one year after the end of the trial.

22 Monitoring plan for the trial

The trial will be monitored according to the monitoring plan agreed and written by the Sponsor, based on the internal risk assessment procedure. Where appropriate the CI will be asked to complete a copy of the Sponsor's self-monitoring template. It is the responsibility of the CI to ensure this is completed and submitted to the RO on request (see Study Monitoring Plan). It is the responsibility of the RO to determine the monitoring risk assessment and explain the rationale.

For multi-centre studies sponsored by RB&HFT the PI at each site may also be required to complete this self-monitoring template and return the form at the frequency determined by the Sponsor, to the RO for review. It is the RO's responsibility to ensure that any findings identified in a PI's monitoring report are actioned in a timely manner and any violations of GCP or the protocol reported to the RO immediately.

Any urgent safety measures at either the CI or a PI site must be reported by that site Investigator within 3 days, as per UK Regulations.

The CI will be provided with a copy of the study monitoring report during the Trial Initiation monitoring visit.

23 Finance

This study is being support by the Moulton Charity. Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care.

24 Insurance and indemnity

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate. The provision of such indemnity for negligent harm should be stated to the participant.

25 Publication policy

Data ownership rights will lie with the institution. Our expectation is that after data analysis, information from this study will be widely disseminated in the medical and scientific community. This will be achieved through a series of peer reviewed publications and meeting

abstracts at local, national and international events. Information will also be distributed more informally through discussion with collaborators. We have a good track record of having research highlighted in regional, national and international media.

26 Statement of compliance

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 2018, the Medicines Act 1968, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the NHS Research Governance Framework for Health and Social Care (Version 2, April 2005, as amended).

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards and UK Clinical Trials Regulation. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

All members of staff working on this study will have suitable qualifications, experience and training in order to carry out the tasks delegated to them. It will be ensured that all members of the research team who handle the data are familiar with the policies governing the confidentiality and security of the data collected during the study and SOPs specific to the study will be adhered to.

27 List of Protocol appendices

Appendix 1 *Schedule of Events*

Appendix 2 *Contraceptive guidance and collection of pregnancy information*

28 References

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Appendix 1: Summary chart of study assessments. Highlighted columns are visits that will be conducted in person.

	Pre-screening Visit	Baseline Screening & Randomization Visit (Treatment 1)		Follow up Visit 1			Crossover Visit (Treatment 2)		Follow up Visit 2		EOS Visit	Unscheduled
Visit	REMOTE	1	1a	2 REMOTE	2a		3	3a	4	4a	5 REMOTE	
Treatment day	-28 to -1	0	1	14	15		22	23	36	37	50-64	
				(+/- 1 day)			(+/- 1 day)		(+/- 1			
PIS and ICF sent to potentially eligible patients	x											
Verbal consent obtained over the phone	x											
Informed consent		x										
Demographics		x										
Medical history		x										x
Review of concomitant medications		x		x			x		x			x
Adverse events review		x		x			x		x		x	x
Physical examination		x										x
Spirometry and gas		x										x
Cough VAS at screening		x										
Inclusion/exclusion criteria		x										
Vital signs – body temperature, heart rate, blood pressure, O_2 saturation and respiratory		x					x		x			x
ECG (optional)												x
Routine bloods (FBC, renal and liver)		x										x
Blood for DNA, RNA, biomarkers		x										
Pregnancy test **α**		x							x			
QoL questionnaires **β**		x		x			x		x			
Global impression of change				x					x			
Randomisation		x										
IMP dispensing		x					x					
Commence IMP			x					x				

WASH OUT – 7 DAYS

IMP reconciliation							x		x			
IMP compliance				x								
Attach cough monitor and		x		x			x		x			
Provide pre-paid envelope		x		x			x		x			
Patient to return cough monitor and Fitbit in pre-			x		x			x		x		
Post out cough monitor, Fitbit and pre-paid envelope (after receipt of cough monitor and Fitbit in time for visit 2)			x									
Telephone call	x		x	x	x			x		x	x	
α- for women of child bearing potential												
β- send electronic link *via* eCRF, includes Cough VAS, L-IPF, K-BILD, Dyspnoea-12, LCQ, HADS												
† - lung function performed within the last 12 months is acceptable												
¥ - for visit 1, 3 & 4 a member of the research team will attach monitor and Fitbit, for visit 2 the patient will attach the devices themselves												

Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

a) Premenarchal
b) Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
medical records, medical examination, or medical history interview.

c) Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT for allow confirmation of postmenopausal status before study enrolment.

Contraception Guidance

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 7.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 2 when having penile-vaginal intercourse with a woman of childbearing potential.

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penivaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
Men must refrain from donating sperm for duration of study and for 90 days after study completion.

Female participants

Female participants of childbearing potential are not eligible to participate.

Table 2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: ▪ Oral ▪ Intravaginal ▪ Transdermal.
Progestogen-only hormonal contraception associated with inhibition of ovulation ▪ Injectable.
Highly Effective Methods That Are User Independent
▪ Implantable progestogen-only hormonal contraception associated with inhibition of ovulation ▪ Intrauterine device (IUD) ▪ Intrauterine hormone-releasing system (IUS) ▪ Bilateral tubal occlusion.
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).*
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with a local regulation regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

Women should only be included after a negative highly sensitive urine or serum pregnancy test within seven (7) days of the first dose of IMP.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while participating in this study. This applies only to participant who received study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Sponsor within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Sponsor.

- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedures.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to Sponsor. Generally, follow-up information will not be required for longer than 6 – 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- An SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Sponsor as described in Section 15 of this protocol. While investigator is no obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be withdrawn from the study.