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A study to find out if orvepitant is safe to use and reduces the severity of cough in patients with idiopathic pulmonary fibrosis

Submission date
25/02/2022

Recruitment status
No longer recruiting

Registration date
09/05/2022

Overall study status
Completed

Last Edited
11/06/2024

Condition category
Respiratory

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
This clinical trial will be conducted in the USA, Europe and the UK, at approximately 30 sites, 10 of which are planned to be in the UK. This trial examines the efficacy and safety of the study medication, orvepitant (2 dose levels), compared to placebo, as a treatment for chronic cough in patients with idiopathic pulmonary fibrosis (IPF), a rare, progressive condition in which the lungs become scarred and breathing becomes increasingly difficult. Approximately 88 participants may be enrolled, but this may be increased to 108 depending on the variance in emerging data.

Who can participate?
Male and female subjects 40 years of age or above, with IPF.

What does the study involve?
The study will start with a screening period of up to 28 days to determine participants' eligibility after which eligible subjects will be randomised to one of two dose groups (Cohorts). All participants will receive both orvepitant and placebo in two different 4 week treatment periods in a cross-over design. Participants in Cohort 1 will receive 30 mg orvepitant and placebo (in a random order), and those in Cohort 2 will receive 10 mg orvepitant and placebo, again in a random order. All study medication will be a once daily tablet taken for 4 weeks. There will be a wash-out period of 3 weeks between the two treatment periods during which no study medication is taken. Neither the participants, nor the study doctor and their team will know what dose group the participant was allocated to, or the order in which treatment was taken (double-blind). Participants will complete a daily electronic diary throughout the study to record the severity of their cough and other symptoms, and will complete several questionnaires relating to their cough and general well-being at the clinic visits. They will also wear a cough frequency monitor for three 24 hour periods during the study. Routine safety assessments will be undertaken including ECGs, blood and urine sampling and lung function tests. There are 8 visits in total. Six of these are clinic visits and two are video or phone calls.

What are the possible benefits and risks of participating?
The study visits will provide the benefit of more frequent health monitoring, and the cross-over

study design means that all subjects will receive active treatment for 4 weeks. Orvepitant is an investigational drug that has been given to around 900 study participants to date. Possible adverse reactions identified so far are mild to moderate somnolence, fatigue and dizziness. Participants are advised not to drive or operate machinery if they experience these reactions. Other, as yet unknown, adverse reactions are possible. Completion of a daily eDiary has the potential to be burdensome. However, the eDiary has been designed to be simple to use and completion should take no more than a few minutes each day. Ambulatory cough monitoring requires a small monitor to be worn for 24 hours which, while not uncomfortable, some patients find cumbersome. Collection of blood samples may be uncomfortable and worst case, may lead to bruising, pain and in very rare cases, infection. Only suitably trained professionals will conduct these procedures. 12-Lead ECGs will be performed which is painless, but the adhesive tabs of the electrodes attached to the skin may lead to itching or a rash in some participants. Lung function is assessed by spirometry. Patients with IPF are used to blowing into the spirometer but it may occasionally cause dizziness coughing or shortness of breath. The subject interviews are optional and subjects do not have to participate in them if they do not want to.

Where is the study run from?
NeRRe Therapeutics Ltd (UK)

When is the study starting and how long is it expected to run for?
February 2022 to June 2024

Who is funding the study?
NeRRe Therapeutics Ltd (UK)

Who is the main contact?
Dr Surinder Birring, surinder.birring@nhs.net

Study website
https://ipf-comfort-study.com/home-patient/

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2021-006278-22

IRAS number
1004546

ClinicalTrials.gov number
NCT05185089

Secondary identifying numbers
ORV-PF-01, IRAS 1004546, CPMS 51434

Study information

Scientific 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

Study objectives
1. To evaluate the effect of orvepitant once daily on cough severity, as perceived by patients, with IPF
2. To evaluate the safety of orvepitant once daily in patients with IPF
3. 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
4. To evaluate the effect of orvepitant on other comorbidities in patients with IPF

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/04/2022, London - Surrey Borders Research Ethics Committee (Equinox House, City Link, Nottingham. NG2 4LA, UK; +44 (0)207 104 8057; surreyborders.rec@hra.nhs.uk), ref: 22/LO/0208

Study design
Interventional double-blind randomized parallel group placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Chronic cough in patients with lung fibrosis of unknown cause

Interventions
All participants will start with a screening period of between 2 and 4 weeks, after which eligible participants will be randomised to one of two dose groups (cohorts) using an interactive web response system. All participants will receive both orvepitant and placebo in two different 4 week treatment periods in a cross-over design. Cohort 1 will evaluate a 30 mg orvepitant dose and Cohort 2 a 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. Following the completion of Treatment Period B, there will be a 2-week follow-up period, making the total study duration for a participant between 15 and 17 weeks.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Orvepitant

Primary outcome measure
Weekly average of the daily IPF Coughing Severity Scale score from Baseline (the last 7 days prior to randomisation) to Week 4 (the last 7 days of treatment)

Secondary outcome measures
1. IPF Coughing Severity Scale. Mean change from Baseline to Week 2 in weekly average of the daily IPF Coughing Severity Scale
2. Early morning cough scale. Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily early morning cough scale
3. 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
4. Urge to cough scale. Mean change from Baseline to Weeks 2 and 4 in weekly average of the

daily urge to cough scale
5. Cough frequency scale. Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily cough frequency scale
6. Dyspnoea scale. Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily dyspnoea scale
7. 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
8. 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
9. Cough frequency measured using the Leicester Cough Monitor ambulatory cough monitor
9.1. Mean change from Baseline to Week 4 in 24-hour cough frequency
9.2. Mean change from Baseline to Week 4 in awake cough frequency
9.3. Mean change from Baseline to Week 4 in night-time cough frequency
9.4. Mean change from Baseline to Week 4 in the number of coughing bouts
10. Leicester Cough Questionnaire (LCQ). Mean change from Baseline to Week 4 in LCQ total and domain (Physical, Social, Psychological) scores
11. King's Brief Interstitial Lung Disease health status questionnaire (KBILD)
11.1. Mean change from Baseline to Week 4 in K-BILD total and domain (Psychological, Breathlessness and Chest Symptoms) scores
11.2. Proportion of patients with a clinically relevant improvement in total KBILD score
12. PROMIS SF SD 8b sleep assessment questionnaire. Mean change from Baseline to Week 4 in the PROMIS SF SD 8b score
13. Hospital Anxiety and Depression Scale (HADS) questionnaire. Mean change from Baseline to Week 4 in the HADS score
14. Hull Airway Reflux Questionnaire (HARQ). Mean change from Baseline to Week 4 in HARQ score

Overall study start date
23/02/2022

Completion date
30/06/2024

Eligibility

Key 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 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 (Hbcorrected DLCO) ≥25% within 12 months of the screening visit
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 antitussive treatment, and which has been present for at least 8 weeks prior to screening
9. Mean daily IPF Coughing Severity Scale score ≥5.0 during the second week of the baseline assessment period (assessed at Visit 2)
10. If taking pirfenidone or nintedanib, the dose must have been stable dose for at least 3 months prior to Screening

Participant type(s)
Patient

Age group
Adult

Lower age limit
40 Years

Sex
Both

Target number of participants
88, with the possibility to increase to 108 following a sample size re-estimation

Total final enrolment
80

Key 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 than the extent of fibrosis according to the reported results of the most recent scan
5. Mean early morning cough scale score ≥5.0 and rest of the day cough scale score <5 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
8. Inability to comply with the use of prohibited and allowed medications as described below:
8.1. Strong or moderate inhibitors of CYP3A4 are not allowed from Screening until 1 week after the last dose of study medication
8.2. Strong or moderate inducers of CYP3A4 are not allowed from Screening until 1 week after the last dose of study medication
8.3. Strong or moderate P-glycoprotein inhibitors are not allowed from Screening until 1 week after the last dose of study medication
8.4. Angiotensin converting enzyme (ACE) inhibitors are not allowed within 3 months of Screening and throughout Part 1
8.5. e. Other treatments for cough management (including opioids, dextromethorphan, gabapentin, pregabalin, baclofen, antihistamines, thalidomide 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.
8.6. The use of other NK1 antagonists (eg aprepitant, fosaprepitant, rolapitant) is not permitted for any reason from 4 weeks before the Baseline visit until completion of Visit 8
8.7. Immune-suppressant drugs and systemic corticosteroids taken for comorbidities 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 Part 1. Any other use is prohibited
8.8. 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

Date of first enrolment
25/03/2022

Date of final enrolment
30/09/2023

Locations

Countries of recruitment
England

Netherlands

United Kingdom

United States of America

Study participating centre
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Sponsor type
Industry

Funder(s)

Funder type
Industry

Funder Name
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Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Other publication
Submission to regulatory authorities

Results will be published at a scientific conference and/or in a peer-reviewed journal in a timely manner consistent with academic standards. The Chief Investigator & NeRRe will be responsible for assembling the publication without delay. Publication or presentation (manuscript, abstract or poster) initiated by an Investigator for submission to a journal or scientific meeting will be facilitated by NeRRe with due consideration of whether such publication may compromise NeRRe's IP rights.

Intention to publish date

30/06/2025

Individual participant data (IPD) sharing plan

The datasets generated during the current study will be available upon request from info@nerretherapeutics.com to academic researchers who have a bona fide reason to request them. Only aggregated data will be provided as participants did not give consent for subject level data to be provided to parties other than NeRRe. Requests for data should include a summary of the research project including its objectives, the funding source, the role of the study data in achieving these objectives, the proposed analysis methods and publication plans.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	04/04/2022	28/12/2022	No	Yes
HRA research summary			28/06/2023	No	No