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

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Primary objectives:• To evaluate the effect of orvepitant once daily on cough severity, as perceived by patients, with IPF• To evaluate the safety of orvepitant once daily in patients with IPFSecondary objectives:• To evaluate the effect of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON51793

Source
ToetsingOnline

Brief title
ORV-PF-01 / IPF COMFORT

Condition

- Pulmonary vascular disorders

Synonym
chronic cough, idiopathic pulmonary fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: NeRRe Therapeutics Ltd
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: chronic cough, pulmonary fibrosis

Outcome measures

Primary outcome

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

Secondary outcome

Secondary efficacy endpoints:

• Mean change from Baseline to Week 2 in weekly average of the daily IPF Coughing Severity Scale

• Mean change from Baseline to Weeks 2 and 4 in weekly average of the early morning cough scale

• Mean change from Baseline to Weeks 2 and 4 in weekly average of the rest of the day cough scale

• Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily urge to cough scale

• Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily cough frequency scale

• Mean change from Baseline to Weeks 2 and 4 in weekly average of the daily dyspnoea scale

• Proportion of subjects in each category at Weeks 2 and 4 for each global rating of cough

• Proportion of subjects in each category at Weeks 2 and 4 for each global rating of cough

• Mean change from Baseline to Week 4 in 24-hour cough frequency

• Mean change from Baseline to Week 4 in awake cough frequency

• Mean change from Baseline to Week 4 in night-time cough frequency

• Mean change from Baseline to Week 4 in the number of coughing bouts

• Mean change from Baseline to Week 4 in LCQ total and domain (Physical, Social, Psychological) scores

• Mean change from Baseline to Week 4 in K-BILD total and domain (Psychological, Breathlessness, Chest Symptoms) scores

• Proportion of patients with a clinically relevant improvement in total K-BILD score

• Mean change from Baseline to Week 4 in the PROMIS SF SD 8b score

• Mean change from Baseline to Week 4 in the HADS score

• Mean change from Baseline to Week 4 in the HARQ score

Safety endpoints:

• Change from Baseline in forced vital capacity (FVC), forced expired volume in one second (FEV1), peak expiratory flow rate and vital capacity (VC)

• Number of treatment emergent adverse events

• Number of treatment emergent serious adverse events

• Number of treatment emergent adverse events resulting in treatment

discontinuation

• Severity of treatment emergent adverse events

• Number of treatment emergent related adverse events

• Treatment emergent changes in physical examination will be recorded as

adverse events

• Mean change from Baseline in each vital sign:

- Systolic blood pressure

- Diastolic blood pressure

- Pulse rate

- Temperature

- Arterial oxygen saturation

- Weight

• Mean change from Baseline in each haematology parameter

• Mean change from Baseline in each clinical chemistry parameter

• Shift from Baseline in each urinalysis parameter

• Proportion of subjects with clinically significant abnormal ECG findings

• Proportion of subjects with non-significant abnormal findings

• Change from Baseline in ECG intervals:

- PR

- QT, QTc and QTcF

- RR

- QRS

• Proportion of subjects with maximum absolute QTcF values by category at Week 4

<450, >450 to <480, >480 to <500, >500 msec

• Proportion of subjects with maximum change from Baseline in QTcF values by category at each post-baseline assessment time-point

<0, >0 to <30, >30 to <60, >60 msec

• Clinically significant changes in ECG findings are recorded as adverse events

Biomarker and pharmacokinetic:

• Mean change from Baseline in the concentration of plasma/serum markers of inflammation and fibrosis

• PK exposure-response relationship for the orvepitant group will be carried out on an exploratory basis to examine the possible relationship between clinical efficacy and plasma levels of the drug

Study description

Background summary

Most respiratory diseases associated with cough, such as chronic bronchitis, asthma and acute viral infections, predominantly affect the airways or upper respiratory tract where sensory innervation is dense. By contrast, pathological changes in IPF principally affect the lung parenchyma and alveoli where innervation is sparse. The pathophysiology of cough in IPF is not yet fully understood, but whilst it is most likely multi-factorial in origin, at least in part it is due to development of hypersensitivity in the cough reflex pathway. Possible explanations for the hypersensitivity are that mechanical distortion of the lung, caused by the fibrosis, directly influences afferent nerve fibres, and/or that efferent nerves that inhibit cough are destroyed by the fibrosis. An imbalance between afferent stimuli and the (efferent) responses then results in increased coughing such that minor, and usually innocuous, stimuli such as talking, eating, temperature change and aromas triggers a cough.
The airways are innervated by vagal sensory nerve fibres, some of which evoke coughing when activated. Patients with chronic cough hypersensitivity likely have elevated levels of proinflammatory mediators. Vagal sensory neurons synapse in the brainstem cough centre and connect into circuits that ascend to the higher brain. Among the neuromodulators that are up-regulated in cough

hypersensitivity is SP. It does not appear to be functionally important under normal physiological conditions but SP and the associated NK1 receptor have been implicated in induction and maintenance of peripheral and central cough reflex hypersensitivity.
Orvepitant has been evaluated in two Phase 2 studies in patients with RUCC and has shown clear evidence of benefit in these trials. In both there were statistically significant and clinically relevant improvements in several different measures of cough burden. Orvepitant was well-tolerated with no safety concerns identified at doses up to 30 mg once daily for 12 weeks.
Thus, antagonism of the NK1 receptor with orvepitant has the potential to be a novel, well tolerated and effective treatment for patients with chronic cough hypersensitivity disorders. The anticipated benefits of orvepitant would include rapid and sustained control of cough, together with associated enhanced general quality-of-life.

Study objective

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

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

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

Study design

The study will be a multi-center, double-blind, randomised, placebo-controlled 2-period cross-over study in subjects with chronic cough due to idiopathic pulmonary fibrosis (IPF).
Subjects will participate in one of two cohorts (Cohort 1 and Cohort 2). Cohort 1 will evaluate a 30 mg orvepitant dose and Cohort 2 the 10 mg dose. Within each cohort, subjects will be randomised to receive either orvepitant or placebo in the first treatment period (Treatment Period A) followed by the alternate treatment in Treatment Period B. There will be a wash-out period of 3 weeks between the two treatment periods. Subjects will be randomised 1:1 to each of the two treatment orders and 1:1 to each cohort.

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

Intervention

Subjects will participate in one of two cohorts (Cohort 1 [30 mg] and Cohort 2 [10 mg]). Within each cohort, subjects will be randomised to receive either orvepitant or placebo once daily in the first treatment period (Treatment Period A) followed by the alternate treatment in Treatment Period B.

Study burden and risks

Although the overall incidence is low, more subjects have experienced palpitations during treatment with orvepitant than during treatment with placebo. However, there were no findings in the preclinical safety studies that would suggest that orvepitant is pro-arrhythmic. Nonetheless, subjects participating in studies should undergo periodic ECG evaluation, either as required by the protocol.
Mild or moderate somnolence and fatigue has been reported at a higher incidencein subjects receiving orvepitant than those that received placebo. Subjects who experience somnolence or fatigue should avoid driving or use of machinery.

Other safety findings from clinical studies but which are less clearly due to Orvepitant include:
• palpitations (feeling the heart beating in the chest)
• headache
• paraesthesia (pins and needles)
• diarrhoea
• insomnia (difficulty getting to sleep)
• anxiety and abdominal (stomach) pain

The safety of orvepitant has been evaluated in a comprehensive preclinical safety programme and in clinical studies in more than 900 healthy subjects and patients. The overall risk profile of orvepitant has been shown to be acceptable in the Phase 2 studies and the unmet need in this population and lack of treatment options supports the continued development of orvepitant for the treatment of chronic cough.

Possible discomforts with checks or measurements:
- Blood samples - swelling, pain, redness, bruising or infection in your arm where blood samples are taken. Taking blood samples can also make dizzy or faint.

- The pulmonary function test - it can cause short of breath or dizzy for a moment after the test. It may also make cough.

The subjects will be asked to complete an electronic diary (eDiary) once a day, in the evening for 13 weeks. It should take just a minute or two each day. eDiary includes the following questionnaires:
- IPF Coughing Severity Scale;
- Early Morning Cough Scale;
- Rest of the Day Cough Scale;
- Urge to Cough Scale;
- Cough Frequency Scale;
- Shortness of Breath Scale;

• Health questionnaires:
- Global Rating of Status Questionnaire for Cough Severity - visits 2, 3, 4, 5, 6, 7 and 8;
- Global Rating of Change Questionnaire for Cough Severity - visits 3, 4, 5, 6, 7 and 8;
- Leicester Cough Questionnaire (LCQ) - visits 2, 4, 5 and 7;
- Kings Brief Interstitial Lung Disease (K-BILD) Health Status Questionnaire - visits 2, 4, 5 and 7;
- PROMIS SD SF 8b - a short form questionnaire to assess sleep disturbance - visits 2, 4, 5 and 7;
- Hospital Anxiety and Depression Scale (HADS) - visits 2, 4, 5 and 7;
- Hull Airway Reflex Questionnaire - visits 2, 4 and 7;

• Ambulatory Cough Monitor - subjects will be fitted with an ACM (the Leicester Cough Monitor9 [LCM]) to record cough frequency over 24 hours at Visits 2, 4 and 7.

The total planned duration of participation in the study for an individual subject is up to 17 weeks.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 (Hb-corrected DLCO) >=25% within 12 months of the screening visit1.
6. Arterial oxygen saturation on room air or oxygen >=90% at Screening.
7. Life expectancy of at least 12 months.
8. Cough that is attributed to IPF, which has not responded to anti-tussive treatment, and which has been present for at least 8 weeks prior to Screening.
9. Mean daily IPF Coughing Severity Scale score >=5.0 during the second week of the baseline assessment period (assessed at Visit 2).
10. If taking pirfenidone or nintedanib2, the dose must have been stable dose for at least 3 months prior to Screening.
11. Female subjects must not be of child-bearing potential (i.e., they must be surgically sterilised or post-menopausal3).
12. Male subjects who have partners of child-bearing potential must agree to use a condom from the Baseline visit until 30 days after the last dose of study medication.

Exclusion criteria

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 (World Health Organisation functional class III or IV [and where functional limitation is due to PAH rather than IPF]).
8. A history of clinically relevant drug or alcohol abuse [according to Diagnostic and Statistical Manual of Mental Disorders 5 criteria (or later edition if applicable)] within 6 months before Screening.
9. Any other clinically significant or unstable medical or psychiatric condition that would, in the opinion of the investigator, interfere with the subject*s ability to participate safely in the study.
10. Any malignancy in the past 5 years unless non-invasive and in remission. Any malignancy diagnosed more than 5 years prior to screening must have been in complete remission for at least 5 years. Written approval must be obtained from the Sponsor for a subject with any history of malignancy.
11. Any clinically significant abnormal laboratory test result(s), measured at Screening.
12. Inability to comply with the use of prohibited and allowed medications as described below:
a. Strong or moderate inhibitors of CYP3A4 are not allowed from Screening until 1 week after the last dose of study medication;
b. Strong or moderate inducers of CYP3A4 are not allowed from Screening until 1 week after the last dose of study medication;
c. Strong or moderate P-glycoprotein inhibitors are not allowed from Screening until 1 week after the last dose of study medication;
d. Angiotensin converting enzyme (ACE) inhibitors are not allowed within 3 months of Screening and throughout the study;
e. Other treatments for cough management (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.
f. 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;
g. Immune-suppressant drugs and systemic corticosteroids taken for co-morbidities are permitted provided the dose has been stable for at least 2 weeks before the screening visit and they are expected to be used at this dose throughout the study. Any other use is prohibited;
h. Supplemental oxygen is permitted provided it has been used for at least 2 weeks before the screening visit and is expected to be used throughout the study;
13. Participation in any clinical research study evaluating another investigational drug or therapy within 30 days or within 5 half-lives (whichever is longer) of the investigational drug prior to Screening. If the subject was in an observational clinical study, no washout is required.
14. Subjects who have previously received orvepitant at any time.
15. Known allergy to any of the excipients used in the investigational medicinal product (IMP) (orvepitant or placebo tablets).
16. Subjects who, in the opinion of the Investigator, should not participate in the study for any other reason.
17. Subjects who are dependent on the Sponsor, CRO or investigator for employment of education.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	23-09-2022
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Orvepitant
Generic name:	NA

Ethics review

Approved WMO Date:	01-06-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-08-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-006278-22-NL
CCMO	NL80512.078.22