A PHASE IIb, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF SILDENAFIL ADDED TO PIRFENIDONE IN PATIENTS WITH ADVANCED IDIOPATHIC PULMONARY FIBROSIS AND INTERMEDIATE OR HIGH PROBABILITY OF GROUP 3 PULMONARY HYPERTENSION.

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This study will evaluate the efficacy, safety, and tolerability of sildenafil or placebo added to pirfenidone treatment (study treatments) in patients with advanced idiopathic pulmonary fibrosis (IPF) and intermediate or high probability of Group 3...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pleural disorders
Study type	Interventional

Summary

ID

NL-OMON43371

Source
ToetsingOnline

Brief title
MA29957 / Esbriet IPF PH

Condition

- Pleural disorders

Synonym
IPF PH

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: IDIOPATHIC PULMONARY FIBROSIS, PIRFENIDONE, PULMONARY FIBROSIS

Outcome measures

Primary outcome

The primary efficacy objective for this study is to evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment in patients with advanced IPF and intermediate or high probability of Group 3 PH. The primary efficacy endpoint will be evaluated based on a comparison of the proportion of patients showing disease progression over 52 weeks of treatment period, as evidenced by reaching the following combined endpoint:

* Relevant decline in 6-minute walk distance (6MWD) of at least 15% from baseline (as defined below*), respiratory-related non-elective hospitalization, or all-cause mortality

* Relevant decline in 6MWD from baseline is defined as:

* Any decline >25% from baseline or

* A decline between 15-25% from baseline, if accompanied by at least one of the

following:

o worsening of oxyhemoglobin (SpO2) desaturation during the 6-minute walk test (6MWT) compared to baseline

o worsening of the maximum Borg scale during the 6MWT compared to baseline

o Increased O2 requirements during the 6MWT compared to baseline

Secondary outcome

Secondary Efficacy Objectives (Full details are given in Protocol Section 6.4.2)

The secondary efficacy objective for this study is to evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment on the basis of the following endpoints:

* Progression-free survival (PFS), defined as the time to decline in 6MWD of >=15% compared with baseline as defined above, respiratory-related non-elective hospitalization, or death from any cause

* Proportion of patients with decline in 6MWD of >=15% from baseline as defined above

* Time to respiratory-related non-elective hospitalization

* Time to death from any cause

* Lung transplantation

* Time to all-cause non-elective hospitalization

* Time to respiratory-related death

* Change from baseline in transthoracic echocardiography (ECHO) parameters

* Change from baseline in pulmonary function tests (PFTs)

* Change from baseline in oxyhemoglobin saturation (SpO2) at rest and during the 6-minute walk test (6MWT)

* World Health Organization (WHO) Functional Class

* Dyspnea (assessed by the University of California San Diego Shortness of

Breath Questionnaire - UCSD SOBQ)

* Health-related quality of life (HRQoL) (assessed by the Saint George*s

Respiratory Questionnaire [SGRQ])

* N-terminal pro-brain natriuretic peptide (NT-proBNP) level

Study description

Background summary

The diagnosis of IPF carries a bleak prognosis, with progressive disability due to respiratory insufficiency (Hallstrand et al. 2005). Pulmonary hypertension is a major contributor to morbidity and mortality in patients with advanced IPF with an adverse impact on survival (Nadrous et al. 2005, Lettieri et al. 2006.). This study is designed to assess the treatment of patients with advanced IPF who have evidence suggesting PH, that is most likely caused by IPF. While drugs used to treat PH have either not been effective for treatment of IPF (bosentan, ambrisentan, macicentan) or are unlikely to be able to address the parenchymal changes in the fibrotic process, anti-fibrotic drugs are unlikely to have any notable effect on the perfusion aspects of interstitial lung diseases (ILDs). Therefore, combination treatment appears as a promising approach to the major clinical problem of combined IPF and PH (Wuyts et al. 2014).
In this study, pirfenidone (Esbriet®) administration will be combined with sildenafil. As sildenafil induces vasodilatation preferentially in well-ventilated lung areas, such vasodilatation could improve ventilation-perfusion matching and thus gas exchange in patients with IPF (Ghofrani et al. 2002). The combination of pirfenidone and sildenafil represents a promising approach to treat patients with advanced IPF and secondary PH.

Study objective

This study will evaluate the efficacy, safety, and tolerability of sildenafil or placebo added to pirfenidone treatment (study treatments) in patients with advanced idiopathic pulmonary fibrosis (IPF) and intermediate or high probability of Group 3 pulmonary hypertension (PH) who are on a stable dose of

pirfenidone with demonstrated tolerability.

Study design

This is a Phase IIb, randomized, placebo-controlled, multicenter, international study of the efficacy, safety, and tolerability of combination treatment with sildenafil and pirfenidone in patients with advanced IPF and intermediate or high probability of Group 3 PH who are on pirfenidone in a dose range of 1602 to 2403 mg/day with demonstrated tolerability. For the purposes of this study, patients have to present with:
* advanced IPF as defined by a measurable pulmonary diffusing capacity (carbon monoxide diffusing capacity [DLCO]) <=40% of predicted value at Screening;
AND
* intermediate and high probability of Group 3 PH as defined by
o mean pulmonary artery pressure (mPAP) >=20 mmHg together with pulmonary artery wedge pressure (PAWP) <=15 mmHg on a previous right heart catheterization (RHC) of acceptable quality
OR
o in the absence of a previous RHC, patients with ECHO showing intermediate or high probability of Group 3 PH, as defined by the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) (Peak tricuspid regurgitation velocity [TRV] >= 2.9 m/s), will be considered eligible for the study, assuming that they meet all other eligibility criteria [Galie et al. 2015]

Intervention

The test products for this study are pirfenidone and sildenafil.
Pirfenidone (5-methyl-1-phenyl-2-1(H)-pyridone) will be administered orally three times per day (TID) with meals, in a range of 1602 to 2403 mg/day. Each pirfenidone capsule contains 267 mg of pirfenidone. Pirfenidone (Esbriet®) will be supplied by the Sponsor as white, hard gelatin capsules printed with *267 mg* in brown ink.
Sildenafil 20 mg will be administered orally TID, about 4 to 6 h apart.
Sildenafil will be supplied by the Sponsor as white, round, biconvex film-coated, tablets. Sildenafil tablets will by encapsulated by a compounding pharmacy to be identical in appearance and size to matching placebo.
Comparator
Placebo will be administered orally TID, about 4 to 6 h apart. Placebo will be supplied by the Sponsor as a capsule with the same appearance and size as the encapsulated sildenafil.

Study burden and risks

Adverse events known to be associated with pirfenidone
Very common (definition: affects more than 10 in every 100 patients)
• anorexia (weight loss)

• headache
• dizziness
• dyspepsia (upset stomach)
• nausea
• diarrhea
• photosensitivity (sunburn)
• rash
• tiredness

Common (definition: affects 1 to 10 patients in 100)
• weight loss
•decreased appetite
• dysgeusia (taste disturbance)
• hot flushes
• Abdominal distention (bloating)
• abdominal discomfort (dyspepsia)
• abdominal pain
• insomnia (difficulty sleeping)
• somnolence (sleepiness)
• constipation (constipation)
• gastroesophageal reflux disease
• vomiting
• concentration increased ALT (liver enzymes)
• increased levels of AST (liver enzymes)
• increased levels of GGT (liver enzymes)
• pruritus (itching)
• arthralgia (joint pain)
• asthenia (weakness)

Uncommon (definition: affects less than 1 in 100 patients)
• angioedema (swelling of the throat or mouth)

Rare but serious (definition: affects less than 1 in 1000 patients)
• agranulocytosis (low white blood cell counts)
• increased total bilirubin concentration in serum (blood) in combination with an elevated concentration of ALT and AST (liver enzymes)

For more risks and side effects, see the informed consent form

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2a Beneluxlaan 2a
Woerden 3440 GR
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2a Beneluxlaan 2a
Woerden 3440 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age 40-80 years (inclusive) at Screening
- Diagnosis of IPF for at least 3 months prior to screening
- Confirmation of IPF diagnosis by the Investigator, in accordance with the 2011 international consensus guidelines, at Screening
- Advanced IPF as defined by a measurable carbon monoxide diffusing capacity/pulmonary diffusing capacity [DLCO] < 40% of predicted value at Screening and intermediate or high probability of Grade 3 PH (as defined in the protocol)
- Prior to the start of Screening, receiving pirfenidone for at least 12 weeks, and on a dose in the range of 1602 to 2403 mg/day for at least 4 weeks prior to the first Screening Visit.
- WHO Functional Class II or III at Screening
- 6MWD of 100 to 450 meters at Screening
- For women of childbearing potential: agreement to remain abstinent or use a non-hormonal contraceptive method with a failure rate <1% per year during the treatment period and for at least 58 days after the last dose of study treatment
- For men who are not surgically sterile: agreement to remain abstinent or use contraceptive measures, and agreement to refrain from donating sperm for at least 118 days after the last dose of study treatment

Exclusion criteria

- History of any of the following types of PH: Group 1 pulmonary arterial hypertension (PAH); Group 2 (left-heart disease); Group 3 (due to conditions other than interstitial lung disease; Group 4 (chronic thromboembolic pulmonary hypertension); Group 5 (other disorders);- History of clinically significant cardiac disease in the opinion of the Investigator;- History of coexistent and clinically significant (in the opinion of the Investigator) COPD, bronchiectasis, asthma, inadequately treated sleep-disordered breathing, or any clinically significant pulmonary diseases or disorders other than IPF or PH secondary to IPF;- Hypotension, autonomic dysfunction, or conditions in which vasodilation may cause an unsafe drop in blood pressure (BP);- History of use of drugs and toxins known to cause PAH

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-02-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Esbriet
Generic name:	Pirfenidone
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	NA
Generic name:	Sildenafil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-10-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2015-005131-40-NL
CCMO	NL59044.056.16