Effects of bosentan on morbidity and mortality in patients with Idiopathic Pulmonary Fibrosis - a multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, group sequential, phase III study

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

Summary

ID

NL-OMON31629

Source
ToetsingOnline

Brief title
Bosentan Use in Interstitial Lung Disease
BUILD-3

Condition

- Respiratory disorders NEC

Synonym
cryptogenic fibrosing alveolitis, idiopathic pulmonary fibrosis

Research involving

Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: bosentan, event driven, idiopathic pulmonary fibrosis, phase III

Outcome measures

Primary outcome

Primary end-point: Time to occurrence of disease worsening or death up to EOS.

- Disease worsening is defined as worsening of PFTs or acute exacerbation of

IPF.

1) Worsening of PFTs (confirmed by two tests at least 4 weeks apart) is defined

as the occurrence of both:

- Decrease from baseline >= 10% in FVC (absolute values, i.e., liters)

and

- Decrease from baseline >= 15% in DLCO (absolute values, i.e., ml.mmHg -1.min-1)

2) Acute exacerbation of IPF is defined as:

An unexplained rapid deterioration of patient*s condition within 4 weeks with

an increasing shortness of breath requiring hospitalization and oxygen

supplementation >= 5 liters/min to maintain a resting SaO2 >= 90% or PaO2 >= 55

mmHg (sea level) or 50 mmHg (high altitude).

Secondary outcome

• Proportion of patients who experienced either disease worsening or death at 1

year.

• Change from Baseline to 1 year in Quality of Life assessed by the SF-36 questionnaire (individual dimensions and overall score).

• Change from Baseline to 1 year in Quality of Life assessed by the EQ-5D questionnaire.

• Transition dyspnea index (TDI) at 1 year.

• Time to occurrence of disease worsening up to EOS.

• Time to death up to EOS.

Exploratory Endpoints

• Change from Baseline to EOT and EOS in Quality of Life assessed by the SF 36 questionnaire (individual dimensions and overall score).

• Change from Baseline to EOT and EOS in Quality of Life assessed by the EQ 5D questionnaire.

• Transition dyspnea index at EOT and EOS.

• Proportion of patients who improve in TDI with at least 1 unit at 1 year.

• Change from baseline to 1 year, EOT, and EOS in PFTs (FVC, DLCO).

• Time to occurrence of disease worsening or death up to EOS in the pooled BUILD 1 (patients diagnosed with surgical lung biopsy) and BUILD 3 patient population.

Study description

Background summary

Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis, is a distinct clinical disorder belonging to the spectrum of interstitial lung diseases (ILD). IPF is a progressive disease characterized by the presence of a histological pattern of usual interstitial pneumonia (UIP) on

surgical lung biopsy.
IPF was considered a chronic inflammatory disease resulting in parenchymal fibrosis. However, recent evidence suggests a mechanism of abnormal wound healing, with progressive extracellular matrix accumulation, decreased fibroblast-myoblast cell death, continuous epithelial cell apoptosis and abnormal re-epithelialization. Progressive fibrotic tissue deposition in the interstitial areas of the lung leads to decreased lung compliance and reduced gas exchanges.
The onset of symptoms is usually gradual and patients complain of non-productive cough, shortness of breath occurring first on exercise and then at rest. Cyanosis, cor pulmonale, and peripheral edema may be observed in the late phase of the disease.
No therapies have been shown to improve the survival or quality of life for patients with IPF and none is registered. Current treatment is still based on the former assumption that IPF is an inflammatory process with concurrent remodeling of the lung by fibrosis. Consequently, it involves anti-inflammatory therapy, including corticosteroids (e.g., prednisone, prednisolone), immunosuppressive/cytotoxic agents (e.g., azathioprine, cyclophosphamide) or a combination of both. However, because of the marginal benefit and serious side effects of the current therapies, along with newer insights into the pathogenesis of IPF, there is an important need for novel therapeutic approaches.

Study objective

The objective of this trial is to demonstrate that bosentan delays disease worsening or death in patients with IPF.

Study design

This is a prospective, randomized, multicenter, double-blind, parallel group, placebo-controlled, event-driven, group sequential, phase III superiority study. The BUILD 3 study is designed to assess the efficacy and safety of bosentan 125 mg b.i.d. in patients with IPF. Eligible patients will be randomized to receive bosentan or placebo (2 : 1, bosentan : placebo). No drug has been approved for the treatment of IPF. At least 390 patients will be enrolled.
The double-blind treatment period is of variable duration. Patients will be called for an End of Study visit when 131 events have been observed. Two efficacy interim analyses are planned after the 50% and 75% of the planned events have been observed. The study will be terminated for superiority of one treatment or for futility (binding), i.e., if the appropriate nominal critical boundaries are crossed.Patients will be followed-up until the BUILD 3 EOS visit and for 28 days after study drug discontinuation. If the patient experiences a documented disease worsening the investigator must permanently discontinue the double-blind study drug.

Intervention

Bosentan 62.5 mg b.i.d. administered orally for 4 weeks, followed by the maintenance dose of 125 mg b.i.d. (62.5 mg b.i.d. if body weight < 40 kg/90 lb).

Or

Placebo

At any time and for tolerability reasons, the double-blind study drug can be down-titrated to 62.5 mg b.i.d.

Study burden and risks

At screening the following assessments will be done: a full medical examination, pulmonary function tests, arterial blood gas and laboratory tests. An electrocardiogram (ECG), and a HRCT scan will only be performed if not done within the last three months prior to randomisation. A Pregnancy test for women of childbearing capacity will be performed monthly and up to 3 months after End Of Treatment.
The initial diagnosis (done by the pathologist) is to be documented by a surgical biopsy < 3 years. No surgical biopsy should be taken for the sole sake of BUILD-3 participation.
Risks associated with participation i.e. the use of bosentan are abnormal liver function tests, and transient low hemoglobin levels. Therefore, all patients will have monthly blood samples taken for LFT monitoring. Hemoglobin will be monitored monthly up to Month 4, every 4 months thereafter up to End Of Treatment. There is a risk of bruising or pain, at the site from where the blood was drawn.
Every 4 months, patients will be seen at the outpatient*s department, for a physical examination, pulmonary function test and to take some blood samples. See also protocol page 22, Visit and Assessment Schedule.
There is no guarantee that patients will benefit directly from this research. Information obtained during the course of this clinical research study may contribute to a better understanding of the disease and may be useful in selecting medicines for future treatment. Regardless of any individual benefit, the knowledge gained from this study may contribute to information that would allow the use of this drug or similar drugs in later treatment for patients suffering from IPF.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Signed informed consent.
•Male or female patients aged 18 years or older (females of child-bearing potential must have been surgically sterilized or use a reliable method of contraception).
•Proven diagnosis of IPF according to ATS/ERS statement, of < 3 years, with surgical lung biopsy (SLB).

Exclusion criteria

•Interstitial lung disease due to conditions other than IPF.
•Presence of extensive honeycomb (HC) on Baseline high-resolution computed tomography (HRCT) scan.
The patient is not allowed in BUILD 3 if HC involves more than 5 % of the parenchyma in 3 or more of the 6 zones (i.e., right and left lung, viewed at the levels of tracheal carina, inferior pulmonary veins, and 1 cm above the dome of the diaphragm), whether the involvement is unilateral or bilateral.
•Severe concomitant illness limiting life expectancy (< 1 year).
•Severe restrictive lung disease: forced vital capacity (FVC) < 50% predicted, or FVC < 1.2

liter.
•Diffusing capacity of the lung for carbon monoxide (DLCO) < 30% predicted.
•Residual volume * 120% predicted.
•Obstructive lung disease: forced expiratory volume in 1 second (FEV1)/FVC < 0.65.
•Documented sustained improvement of patient's IPF condition up to 12 months prior to randomization with or without IPF-specific therapy.
•Recent pulmonary or upper respiratory tract infection (up to 4 weeks prior to randomization).
•Acute or chronic impairment (other than dyspnea) limiting the ability to comply with study requirements (e.g., pulmonary function tests).
•Chronic heart failure with NYHA class III/IV or known left ventricular ejection fraction < 25%.
•ALT/SGPT and/or AST/SGOT > 1.5 times the upper limit of the normal ranges (ULN).
•Moderate to severe hepatic impairment, i.e., Child-Pugh Class B or C.
•Serum creatinine >= 2.5 mg/dl (221 *mol/l) or chronic dialysis.
•Hemoglobin concentration < 75% the lower limit of the normal ranges.
•Systolic blood pressure < 85 mmHg.
•Pregnancy or breast-feeding.
•Current drug or alcohol dependence.
•Chronic treatment with the following drugs prescribed for IPF (within 4 weeks of randomization):
- Oral corticosteroids (> 20 mg/day of prednisone or equivalent),
- Immunosuppressive or cytotoxic drugs,
- Antifibrotic drugs including pirfenidone, D-penicillamine, colchicine,TNFalfa blocker, imatinib, interferon *, cyclophosphamide, azathioprine,
- Chronic use of N-acetylcysteine (prescribed for IPF).
•Oral anticoagulants other than those indicated for a venous or arterial thrombotic disease.
•Treatment with glibenclamide (glyburide) and calcineurin inhibitors (cyclosporine A, tacrolimus) up to 1 week prior to randomization.
•Treatment with an endothelin receptor antagonist up to 3 months prior to randomization.
•Participation in the BUILD 1 trial.
•Treatment with another investigational drug up to 3 months prior to randomization or planned treatment.
•Known hypersensitivity to bosentan or any of the excipients.

Study design

Design

Study phase:	3
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):	10-04-2007
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tracleer
Generic name:	bosentan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-12-2006
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-03-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-11-2007
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-04-2008

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-06-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-04-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-08-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	15-12-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-01-2010
Application type:	Amendment
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	EUCTR2006-001183-24-NL
CCMO	NL14521.078.06