A double blind, randomised, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)

Published: 24-08-2015
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The objective of the trial is to assess the efficacy and safety of nintedanib in the treatment ofSSc with ILD at a dose of 150 mg bid compared to placebo.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON47379

Source
ToetsingOnline

Brief title
Nintedanib in SSc-ILD

Condition

- Lower respiratory tract disorders (excl obstruction and infection)
- Cornification and dystrophic skin disorders

Synonym
scar formation in the lungs caused by systemic sclerosis, systemic sclerosis associated lung fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim

Intervention

Keyword: efficacy, nintedanib, safety, sclerosis

Outcome measures

Primary outcome

to demonstrate a reduction in the annual rate of decline in FVC in

mL over 52 weeks in the nintedanib treatment group compared to the placebo

group

Secondary outcome

The main secondary objectives are to demonstrate efficacy in regard to skin

fibrosis as

assessed by the modified Rodnan Skin Score at week 52 and to demonstrate an

improvement

of patient*s symptoms as measured by the SGRQ (Saint George*s Respiratory

Questionnaire)

total score at week 52.

Other objectives are to assess safety and tolerability, mortality, the effects

on different

systemic organ manifestations of SSc, pharmacokinetics and the effects of

nintedanib on

patient*s perception of his/her disease.

Study description

Background summary

As no approved SSc-ILD treatment is available, and internal organ fibrosis, especially lung
fibrosis, leads to severe loss of function and ultimately results in death, there is a high unmet
medical need to stop the fibrotic remodeling and thus prevent loss of organ function.
As a common practice, immunosuppressive agents (e.g. mycophenolate mofetil, cyclophosphamide, methotrexate, azathioprine, prednisone) are widely used to address the
organ-specific manifestations. Currently no approved treatment is available addressing the
interstitial lung manifestation of the disease.
Based upon the mechanism of action and the similarities of pathophysiology resulting in the
same pro-fibrotic cascade described in both SSc-ILD and IPF (P14-07919), the pharmacological rationale for multiple tyrosine kinase inhibition in SSc-ILD is sound and
promising. Pre-clinical evidence of anti-fibrotic activity of nintedanib in SSc and clinical
evidence in IPF with an acceptable safety profile support the rationale of performing a trial in
patients with SSc-ILD.
SSc-ILD is expected to be a co-manifestation with varying degrees of involvement of skin
and other organs. From a mechanistic point of view and based on preclinical data, an effect of
nintedanib on manifestations of the disease outside of the lung, for example skin effects, is
also expected.
The rationale to conduct this Phase III trial in SSc-ILD can be summarized as follows:
High unmet medical need
Preclinical evidence for efficacy in SSc and SSc-ILD
Anti-fibrotic efficacy of nintedanib proven in IPF patients (similar pattern regarding
lung fibrosis)
From a mechanistic point of view, treatment with nintedanib may also be beneficial

on the disease outside of the lung, for example skin.

Study objective

The objective of the trial is to assess the efficacy and safety of nintedanib in the treatment of
SSc with ILD at a dose of 150 mg bid compared to placebo.

Study design

multi-centre, multi-national, prospective, double blind, randomised, placebo controlled.

Intervention

56 to 104 weeks of treatment, witht nintedanib 150 mg twice daily or placebo 150 mg twice daily.

Study burden and risks

Blood samples (every visit), pregnancy test in blood or urine (every visit), PK assessment (2 visits), ECG (4 visits), filling in 6 questionnaires (4 visits), maintaining menses calendar (every visit), filling in PK card (12 times over 6 days), mRSS assessment (7 visits), digital ulcer assessment (7 visits), autoantibody assessment (3 visits), biomarker blood sample (4 visits), farmacogenomic blood sample (1 visit), SpO2 test (4 visit), spirometry (12 visits), DLCO test (5 visits), echo of the hart (2 visits). If necessary a HRCT scan; when no HRCT is available, less than 1 year old.

The risks of treatment with nintedanib have been well delineated in patients with the fibrotic lung disease IPF. These risks are primarily related to the gastrointestinal tract (nausea, vomiting, diarrhoea, abdominal pain), and are usually managed with supportive therapy and
with temporary or permanent dose reduction to 100 mg bid. In some cases, temporary interruption or permanent drug discontinuation is necessary. A reduction in appetite and weight decrease has also been reported in patients treated with nintedanib. Patients with SSc may already suffer from gastrointestinal symptoms and will be monitored for such events. Parenteral fed patients will be excluded from the trial. Increases in liver enzymes and bilirubin have been reported with the use of nintedanib and liver enzymes and must be followed closely during treatment (see also Section 4.2.1.2). Nintedanib must be dose-reduced, or interrupted in the event of hepatic toxicity and further treatment withheld until recovery of the abnormal laboratory parameters.
Risk associated to the HRCT: The more radiation received over the course of a life, the greater risk of having cancerous tumors or of inducing changes in

genes. The changes in genes possibly could cause abnormalities or disease in your future offspring. The radiation in this study is not expected to greatly increase these risks, but the exact increase in such risks is not known. You also may feel uncomfortable in the described tunnel. However, the scanner is open at both ends, and an intercom allows you to talk with the trial doctor and the staff. The scan can be stopped at any time at your request, but the scan may not be complete.

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

- Age >< = 18 years
- 2013 ACR / EULAR classification criteria for SSc fulfilled
- SSc disease onset (defined by first non-Raynaud symptom) within 7

years
- SSc related Interstitial Lung Disease confirmed by HRCT; Extent of fibrotic disease in the lung ><= 10%
- FVC ><= 40% of predicted normal
- DLCO 30% to 89% of predicted normal

Exclusion criteria

- AST, ALT > 1.5 x ULN;- Bilirubin > 1.5 x ULN;- Creatinine clearance < 30 mL/min;- Airway obstruction (pre-bronchodilator FEV1/FVC < 0.7);- Other clinically significant pulmonary abnormalities;- Significant pulmonary hypertension ;- Cardiovascular diseases;- More than 3 digital fingertip ulcers, or a history of severe digital necrosis requiring hospitalization or severe other ulcers at discretion of the investigator.;- Bleeding risk (such as predisposition to bleeding, fibrinolysis, full-dose anticoagulation, high dose antiplatelet therapy, history of hemorrhagic central nervous system (CNS) event within last year;- international normalised ratio (INR) > 2, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) by > 1.5 x ULN);- History of thrombotic event within last year;- Known hypersensitivity to the trial medication or its components (i.e. soya lecithin);- Clinical signs of malabsorption or needing parenteral nutrition;- Previous treatment with nintedanib or pirfenidone;- Treatment with prednisone > 10 mg/day, azathioprine, hydroxychloroquine, colchizine, D-penicillamine, sulfasalazine, cyclophosphamide, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib and ciclosporine A, potassium para-aminobenzoate;- Unstable background therapy with either mycophenolate mofetil or methotrexate ;- Previous or planned hematopoietic stem cell transplantation;- Patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment);- Patient with a history of Scleroderma renal crisis

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):	08-12-2015
Enrollment:	17
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ofev
Generic name:	nintedanib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	24-08-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	24-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-05-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	16-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2018
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	EUCTR2015-000392-28-NL
ClinicalTrials.gov	NCT02597933
CCMO	NL54693.056.15