

# BENEFIT study

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Inhibition of TNF-alpha in IPF (idiopathic pulmonary fibrosis) will affect inflammatory and pro-fibrotic cytokine expression and thereby will slow-down disease progression in IPF

<b>Ethische beoordeling</b>	Positief advies
<b>Status</b>	Werving gestart
<b>Type aandoening</b>	-
<b>Onderzoekstype</b>	Interventie onderzoek

## Samenvatting

### ID

NL-OMON27093

### Bron

Nationaal Trial Register

### Verkorte titel

BENEFIT

### Aandoening

IPF; Idiopathic pulmonary fibrosis; interstitial lung disease; lung fibrosis  
Longfibrose; interstitiele longziekten  
TNF-alpha; anti-TNF-alpha antibodies

## Ondersteuning

**Primaire sponsor:** Investigator's initiated study performed by BENEFIT study group

**Overige ondersteuning:** Centocor BV

Einsteinweg 92

2333 CD Leiden

## Onderzoeksproduct en/of interventie

## Uitkomstmaten

### Primaire uitkomstmaten

Change in FVC from baseline<br>

## Toelichting onderzoek

### Achtergrond van het onderzoek

Idiopathic Pulmonary Fibrosis (IPF) is a relatively rare interstitial lung disease of unknown etiology with a median survival between 2 and 4 years. Treatment of IPF is still a major therapeutic challenge;

standard treatment includes corticosteroids and azathioprine or cyclophosphamide. However, the available studies on standard treatment of IPF have not proven a significant effect on survival.

There is compelling evidence for an important role of tumor necrosis factor-alpha (TNF- $\alpha$ ) in the pathophysiology of IPF. TNF- $\alpha$  has a direct pro-fibrotic potential by stimulation of (myo)fibroblast proliferation and collagen synthesis and its role involves additional activities in regulation of inflammatory and immune responses. In animal models of fibrosis a pivotal role for TNF- $\alpha$  was demonstrated; induction of fibrosis could be inhibited by concomitant treatment with soluble TNF- $\alpha$  receptors.

Therefore, we hypothesize that the inhibition of TNF- $\alpha$  by the chimeric monoclonal anti-TNF- $\alpha$  antibody infliximab (Remicade®) will affect inflammatory and pro-fibrotic cytokine expression and thereby will slow-down disease progression in IPF.

Patients (n=18) treated with standard therapy (prednisolone and azathioprine) for at least three months will be randomly assigned to receive additional intravenous infliximab (5 mg/kg) or placebo at week 0,2,6,12,18,24,30,36,42 and 48.

Primary endpoints are change from baseline in Forced Vital Capacity and time to disease progression according to the ATS criteria. Secondary endpoints include among others analyses of pro-inflammatory and pro-fibrotic mediators and growth factors in bronchoalveolar lavage fluid and serum.

### Doel van het onderzoek

Inhibition of TNF- $\alpha$  in IPF (idiopathic pulmonary fibrosis) will affect inflammatory and pro-fibrotic cytokine expression and thereby will slow-down disease progression in IPF

### Onderzoeksopzet

Clinical assessments

- week 0,14 and 52

- if indicated (time to disease progression)

Bronchalveolar lavage at week 0 and 14

Serum at week 0,14,32 and 52

Blood at week 0,14 and 52

### **Onderzoeksproduct en/of interventie**

Intavenous administration of infliximab (chimeric monoclonal anti-TNF-alpha; 5 mg/kg) vs placebo (2:1) next to standard treatment with prednisolone and azathioprine; given at week

0,2,6,12,18,24,30,36,42, and 48.

## **Contactpersonen**

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### **Wetenschappelijk**

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# Deelname eisen

## Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

### 1. Diagnosis of IPF(2):

- a) If possible a thoracoscopic or open lung biopsy showing UIP. A thoracoscopic or open lung biopsy must be performed in patients <51 years old. Transbronchial biopsy is strongly advocated and should show no features to support an alternate diagnosis.
- b) Insidious onset of otherwise unexplained dyspnea on exertion.
- c) Presence of bibasilar, inspiratory crackles.
- d) Abnormal lung function: VC < 90% predicted or TLC < 90% predicted, plus DLco < 90% predicted.
- e) Parenchymal abnormalities on chest X-ray.
- f) HRCT: bilateral parenchymal abnormalities with peripheral and bibasilar distribution showing linear and reticular opacities, usual in conjunction with subpleural honeycombing and architectural distortion.
- g) Exclusion of other forms of interstitial lung diseases.
- h) In patients > 50 years fulfilling all above mentioned criteria a BAL to exclude other causes of interstitial lung disease is sufficient and a lung biopsy is not necessary.

2. Show stable disease or failure to respond to standard medication (i.e. azathioprine and prednisolone) (as defined by the ATS/ERS criteria(2)) during a minimum of 3 months prior to the study, with a minimum dose of prednisolone (or equivalent) of 20 mg daily, and azathioprine 2 mg per kg with a maximum of 200 mg daily during 3 months.

3. Men and women between 40 and up until 79 years.

4. Diagnosis of IPF within the past 36 months

5. Men and women must use adequate birth control measures (eg, abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) for the duration of the study and should continue such precautions for 6 months after receiving the last infusion.

6. The screening laboratory test results must meet the following criteria:
  - a. Haemoglobin > 8.5 g/dL (5.3 mmol/L)
  - b. WBC >  $3.5 \times 10^9/L$
  - c. Neutrophils >  $1.5 \times 10^9/L$
  - d. Platelets >  $100 \times 10^{12}/L$
  - e. SGOT (AST) and alkaline phosphatase levels must be within 3 times the upper limit of normal range for the laboratory conducting the test.
7. Patient must be able to adhere to the study visit schedule and other protocol requirements.
8. Patient must be able to communicate meaningfully with the study personnel.
9. The patient must be capable of giving informed consent and the consent must be obtained prior to any screening procedures.
10. Must have a chest radiograph within 3 months prior to first infusion with no evidence of malignancy or infection.
11. Are considered eligible according to the tuberculosis (TB) eligibility assessment, screening, and early detection of reactivation rules defined in Section 4.3

### **Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)**

1. Critical low lung function: FVC < 50%.
2. Artificially ventilated.
3. Inability to undergo a broncho-alveolar lavage.
4. Patients that were treated with IFN-alpha
5. Women who are pregnant, nursing, or planning pregnancy within 1,5 years after screening (ie, approximately 6 months following last infusion).
6. Use of any investigational drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.
7. Treatment with any other therapeutic agent targeted at reducing TNF (eg, pentoxifylline, thalidomide, etanercept, adalimumab etc.) within 3 months of screening.

8. Previous administration of infliximab.
9. History of receiving human/murine recombinant products or known allergy to murine products.
10. Serious infections (such as pneumonia or pyelonephritis) in the previous 3 months. Less serious infections (such as acute upper respiratory tract infection [colds] or simple urinary tract infection) need not be considered exclusions at the discretion of the investigator.
11. Documented HIV infection.
12. Active hepatitis- B or hepatitis-C.
13. Are considered ineligible according to the TB eligibility assessment, screening, and early detection of reactivation rules defined in Section 4.3.
14. Have or have had an opportunistic infection (eg, herpes zoster [shingles], cytomegalovirus, *Pneumocystis carinii*, aspergillosis, histoplasmosis, or mycobacteria other than TB) within 6 months prior to screening.
15. Have current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, cardiac, neurologic, or cerebral disease (including demyelinating diseases such as multiple sclerosis).
16. Concomitant congestive heart failure and/or cor pulmonale, including medically controlled asymptomatic patients. Criteria for cor pulmonale are based on cardiac sonography: estimated systolic pulmonary artery pressure > 40 mmHg at rest.
17. Presence of a transplanted organ (with the exception of a corneal transplant > 3 months prior to screening).
18. Malignancy within the past 5 years (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence).
19. History of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (such as nodes in the posterior triangle of the neck, infra-clavicular, epitrochlear, or periaortic areas), or splenomegaly.
20. Known recent substance abuse (drug or alcohol).
21. Poor tolerability of venipuncture or lack of adequate venous access for required blood sampling during the study period.
22. Have a chest radiograph at screening that shows evidence of malignancy, infection, or any abnormalities suggestive of TB as described in Section 4.3.2.1

## Onderzoeksopzet

### Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blinding:	Dubbelblind
Controle:	Placebo

### Deelname

Nederland	
Status:	Werving gestart
(Verwachte) startdatum:	01-07-2004
Aantal proefpersonen:	18
Type:	Verwachte startdatum

## Ethische beoordeling

Positief advies	
Datum:	12-04-2008
Soort:	Eerste indiening

## Registraties

### Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

### Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

## In overige registers

Register	ID
NTR-new	NL1229
NTR-old	NTR1274
Ander register	MEC : 04/043
ISRCTN	ISRCTN wordt niet meer aangevraagd

## Resultaten

### Samenvatting resultaten

N/A