A Phase 2, Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging Study Evaluating the Efficacy and Safety of CNTO 888 Administered Intravenously in Subjects with Idiopathic Pulmonary Fibrosis

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

Summary

ID

NL-OMON37285

Source
ToetsingOnline

Brief title
CNTO888PUL2001

Condition

- Pleural disorders

Synonym
Idiopathic Pulmonary Fibrosis, lungfibrosis, usual interstitial pneumonia (UIP)

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Centocor Inc.

Intervention

Keyword: CNTO 888, Efficacy and Safety, Idiopathic Pulmonary Fibrosis

Outcome measures

Primary outcome

The primary endpoint of this study is the rate of percent change (relative to

baseline per 4-week interval) in FVC through Week 52.

Secondary outcome

The major secondary endpoints include:

* Time to disease progression (defined as the time from randomization to

occurrence of 1 of the

following events, whichever occurs first: acute IPF exacerbation, lung

transplantation, and/or all cause

mortality) through Week 52.

* Absolute change from baseline in FVC (mL) at Week 52.

* Relative change from baseline in DLCO at Week 52.

* Change from baseline in St. George*s Respiratory Questionnaire total score at

Week 52.

Study description

Background summary

In vitro and in vivo research confirms the hypothesis that CCL2 plays een important role in fibrosis. CNTO 888(Anti-CCL2 monoclonal antibody) can be an effective agent for the treatment of IPF by neutralizing the profibrotic activity of CCL2.

Study objective

The primary objective is to determine the efficacy (as measured by pulmonary function) and safety of CNTO 888 in subjects with IPF. The major secondary objectives are to assess the
effect of CNTO 888 on measures of disease progression, to assess the effect of CNTO 888 on patient
reported outcomes, functional capacity measurements, and health-related quality of life in subjects with
IPF, and to assess the pharmacokinetics and pharmacodynamics of CNTO 888 in subjects with IPF.

Study design

This is a Phase 2, multicenter, multinational, randomized, double-blind placebo-controlled, parallel-group, dose-ranging study in subjects with IPF.

Intervention

Subjects will be randomly assigned to 1 of 4 treatment groups in a 1:1:1:1 ratio. Subject allocation to treatment group will be performed using a permuted block randomization
stratified with the following strata: (1) high-risk category (yes/no), and (2) baseline oral corticosteroid
use (yes/no).
Group 1 (n = 30): Placebo intravenous (IV) infusion every 4 weeks (q4w), from Week 0 through
Week 48.
Group 2 (n = 30): CNTO 888 1 mg/kg IV infusion q4w, from Week 0 through Week 48.
Group 3 (n = 30): CNTO 888 5 mg/kg IV infusion q4w, from Week 0 through Week 48.
Group 4 (n = 30): CNTO 888 15 mg/kg IV infusion q4w, from Week 0 through Week 48
The study will enroll and treat the first 20 subjects (with 3 doses of study agent), as part of a safety
run-in, in a subset of sites. These subjects will be randomized in a 1:1:1:1 ratio to placebo, 1 mg/kg,
5 mg/kg, or 15 mg/kg CNTO 888. A formal Data Monitoring Committee (DMC) review will occur
following this safety run-in, and will recommend whether or not enrollment may be opened up to the rest

of the sites.

Route of Administration: IV infusion
Interval Between First and Last Dose of Active Study Agent: 48 weeks
Duration of Study Participation: All subjects will be followed through Week 72, even if the study
drug treatment is prematurely discontinued for any reason.
End of Study Definition: The end of the study is defined as the last visit of the last subject worldwide.
Number of Subjects: Approximately 120 subjects with IPF will be randomly assigned in a 1:1:1:1 ratio
to 1 of the 4 treatment groups, resulting in approximately 30 subjects in each of the 3 active CNTO 888
treatment groups and 30 in the placebo group.
Number of Sites: Approximately 25 sites globally.

Study burden and risks

The patient receives the following examinations:
- Physical examination
- Tuberculosis evaluation including X-ray if nessecary
- DLCO test, if not available within 3 months before the screening visit
- Blooddraw
- Questionnaires
- 'Exhaled Breath Condensate' (EBC) test
- Urine sample
- '6 minute walk test'
- Pulmonary function test
- 'High resolution computed tomography' (HRCT) scan
- Studyagent administration

Possible side-effects of the studyagent could be:
Hypersensitivity, immune response to antibodies, risk of bleeding, exposure to radiation, risk of unknown side-effects of CNTO 888

Despite current treatment IPF remains a progressive, irreversibel and life-threathening disease.
The scientific rationale for anti-CCL2 therapy in the treatment of idiopathic pulmonary fibrosis supports the development of CNTO 888 for this indication. Evaluation of the safety and efficacy of CNTO 888 in the treatment of subjects with idiopathic pulmonary fibrosis is reasonable based on evaluation of the benefits versus the risks observed in the preclinical studies and current data from the first in human Phase 1 oncology study. CNTO 888 may provide an effective treatment for patients with idiopathic pulmonary fibrosis while also providing an acceptable risk / benefit ratio.

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

1. Aged 40 to 80, inclusive.
a. Subjects who are aged 40 years to < 50 years of age at the time of screening will be required to have surgical lung biopsy evidence of UIP in order to be considered eligible for the trial.
2. Physician diagnosis of IPF (according to a modified version of the ATS/ERS criteria; ATS, 2000) within 4 years of screening.
Subjects must meet all of the major criteria and 3 of the 4 minor criteria listed below:
Major criteria (must meet all)
a. Exclusion of other known causes of interstitial lung disease, such as certain drug toxicities, environmental exposures, and connective tissue diseases.
b. Abnormal pulmonary function studies that include evidence of restriction

(reduced vital capacity, often with an increased FEV1/FVC ratio) and impaired gas exchange (increased alveolar-arterial oxygen gradient [P(A-a)O2] or evidence of desaturation at rest or exercise or decreased DLCO).
c. Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT scans.
Minor Criteria (must meet 3)
a. Age > 50 years.
b. Insidious onset of otherwise unexplained dyspnea on exertion.
c. Duration of illness * 3 months.
d. Bibasilar, inspiratory crackles (dry or *Velcro-type* in quality).
3. Have surgical lung biopsy evidence of UIP and/or HRCT scan-based diagnosis of IPF. In the absence of surgical lung biopsy, an HRCT scan obtained within 3 months prior to or at screening must be available for review.
4. Have evidence of progressive IPF disease activity despite current treatment. Progressive IPF disease activity, for the purposes of this protocol, is defined as having 1 or more of the following within the past 12 months:
a. Relative decrease of * 10% in FVC.
b. Relative decrease of * 15% in DLCO.
c. Evidence of clinically significant worsening on HRCT (eg, development of honeycombing, increase in opacities).
d. Significant worsening of dyspnea at rest or with exertion.
5. Evidence of recent stability of percent-predicted FVC (defined as not having changed > 15% at the baseline visit relative to the screening visit).
6. FVC * 50% of the predicted value at screening.
7. Women of childbearing potential must have a negative serum pregnancy test result at screening. Women of childbearing potential and all men must be using adequate birth control measures and must agree to continue to use such measures and not become pregnant or plan a pregnancy until 12 months after receiving the last infusion of study agent.
8. Are considered eligible according to the following TB screening criteria:
a. Have no history of latent or active TB prior to screening.
b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
c. Have had no recent close contact with a person with active TB.
d. Within 2 months prior to the first administration of study agent, have negative diagnostic TB test results (defined as a negative QuantiFERON-TB Gold test).
e. Have a chest radiograph (both posterior-anterior and lateral views) if clinically indicated or HRCT taken within 3 months prior to screening and read by a qualified radiologist, with no clear evidence of current active TB or old inactive TB.
9. Capable of understanding subject assessment forms.
10. Have provided signed, written, informed consent before receiving any protocol specific procedures.
11. Willing to adhere to the study visit schedule and other protocol requirements.

Exclusion criteria

1. Have evidence of interstitial pneumonia other than IPF.
2. Diagnosis of IPF is not confirmed by HRCT or lung biopsy results.
3. Partial pressure of oxygen in arterial blood (PaO2) < 55 mmHg (sea level) or 50 mmHg (altitude) at rest on room air. If arterial blood gas results are not available, an oxygen saturation via pulse oximetry (SpO2) < 88% with O2 supplementation at rest.
4. Known clinically significant pulmonary hypertension requiring vasodilator therapy (eg, calcium channel blockers, prostacyclin or prostacyclin analogs, nitric oxide, adenosine) or chronic anticoagulation therapy.
5. Have a diagnosis of other significant respiratory disorder (eg, asthma, TB, sarcoidosis, aspergillosis, chronic obstructive pulmonary disease [COPD], or cystic fibrosis).
6. Have obstruction on prebronchodilator PFTs (defined as FEV1/FVC < 0.7) at screening.
7. Demonstrate an increase in FEV1 * 12% postbronchodilator.
8. Have a predicted life expectancy less than 1 year.
9. Previous treatment for IPF with an investigational/experimental medication within 6 weeks, or within 5 t1/2 of the investigational/experimental medication, whichever is longer, prior to screening or are participating in another investigative study.
10. Current treatment with sildenafil, IFN-*, mycophenolate, or endothelin receptor antagonists.
11. Current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, cardiac, neurologic, or cerebral disease, or any laboratory abnormality which would pose/suggest a risk to the subject by participation in the study.
12. Known to be seropositive for HIV, known active hepatitis A, B, or C infection, or ALT/SGPT and/or AST/SGOT > 2 times the upper limit of normal at screening.
13. Within 3 months prior to screening, have had a clinically important, serious infection (eg, hepatitis, pneumonia, or pyelonephritis), have been hospitalized for an infection, or have been treated with IV antibiotics for an infection. Less serious infections (eg, acute upper respiratory tract infection or simple urinary tract infection) need not be considered exclusions at the discretion of the investigator.
14. Opportunistic infection (eg, cytomegalovirus, Pneumocystis carinii) within 6 months prior to screening.
15. Received any live attenuated vaccination (eg, FluMist) within 3 months prior to screening or are expected to receive any live attenuated vaccinations during the trial or up to 3 months after the last administration of study agent. Inactivated, injectable influenza and pneumococcal vaccines are permissible.
16. Serious concomitant illness that could interfere with the subject*s participation in the study.
17. History of substance abuse (drugs or alcohol) within the 3 years prior to screening, history of noncompliance to medical regimens, or other condition/circumstance that could interfere with the subject*s adherence to protocol requirements (eg, psychiatric disease, lack of motivation, travel).

18. Major surgery within 1 month prior to screening or planned surgery during the study.
19. Currently listed for lung transplantation.
20. Have any known malignancy or have a history of malignancy within the previous 5 years (with the exception of a nonmelanoma skin cancer that has been treated with no evidence of recurrence for at least 3 months).
21. Have a transplanted organ (with the exception of a corneal transplant > 3 months prior to screening).
22. Known allergies or clinically significant reactions to murine, murine-human chimeric, or human proteins or other components of the product.
23. Significant bleeding diathesis or excessive risk of bleeding, including chronic anticoagulant therapy.

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:	Pending
Start date (anticipated):	01-12-2008
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	CNTO 888
Generic name:	CNTO 888

Ethics review

Approved WMO Date:	07-10-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2008-001281-86-NL
CCMO	NL24850.018.08