ARTEMIS: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel-Group, Event-Driven Study to Evaluate the Efficacy and Safety of Ambrisentan in Subjects with Early Idiopathic Pulmonary Fibrosis (IPF).

Published: 06-02-2009
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Ethical review	Approved WMO
Status	Will not start
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON35478

Source
ToetsingOnline

Brief title
ARTEMIS

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
Idiopathic Pulmonary Fibrosis, lung fibrosis

Research involving

Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: Ambrisentan, Endothelin receptor antagonist (ERA), Idiopathic Pulmonary Fibrosis (IPF)

Outcome measures

Primary outcome

The primary endpoint of this study is as follows:

Time to death or disease progression, defined as the first occurrence of any of

the following:

• Either a decrease of >= 10% in FVC (L) and a decrease of >= 5% in diffuse lung

capacity for carbon monoxide (DLCO) (ml/min/mmHg) or a decrease of >= 5% in FVC

(L) and a decrease of >= 15% in DLCO (ml/min/mmHg); (deterioration in FVC and

DLCO must be confirmed at the subsequent visit within 28 (± 14) days)

• Respiratory hospitalization (as defined in Section 7.10). Events will be

adjudicated by a blinded Endpoint Committee

• All cause mortality.

Secondary outcome

The secondary endpoints of this study are as follows:

• Proportion of subjects with disease progression or death at 48 weeks (Visit 7)

• Change in pulmonary function tests (FVC and DLCO) at Visit 7

• Change in 6 minute walk distance (6MWD) at Visit 7

• Change in QOL score at Visit 7 as assessed by:

o Short Form 36® (SF 36)

o St. George*s Respiratory Questionnaire (SGRQ)

• Change in dyspnea as assessed by change in Transition Dyspnea Index (TDI)

score at Visit 7

• Among subjects without PH at baseline, the proportion who develop PH on study

(documented by RHC)

Study description

Background summary

Idiopathic pulmonary fibrosis is a chronic, fibrosing lung disease of unknown etiology. Most patients die within 3 to 8 years of the onset of symptoms. To date, there is no approved therapy for the treatment of IPF.

Study objective

The primary objective of this study is to determine if ambrisentan is effective in delaying disease progression and death in subjects with IPF.
Secondary objectives include evaluation of the safety and effect of ambrisentan on development of pulmonary hypertension, quality of life (QOL), and dyspnea symptoms in this subject population.
Exploratory evaluations will include changes in other disease related assessments including the United Network for Organ Sharing Lung Allocation Score (UNOS LAS), changes in microRNA expression, changes in pulmonary high resolution computed tomography (HRCT) and biomarkers related to IPF pathogenesis.

Study design

This is a randomized, double blind, placebo controlled, multi center study to evaluate the efficacy and safety of ambrisentan in subjects with IPF.
The study will consist of three periods: screening, titration and treatment. Screening assessments may occur over a period of not more than 28 days. Following screening, all eligible subjects will be stratified based on (1) the presence or absence of pulmonary hypertension on RHC and (2) whether or not a surgical lung biopsy (SLB) has been performed with definite or probable UIP, determined by a core pathologist to confirm diagnosis. Subjects will then be randomized in a 2:1 ratio to receive either ambrisentan or placebo.

Study visits will occur every 84 days (+/* 6 days) from the first treatment visit.
Pregnancy testing will be performed every 28 (± 2) days throughout the study.
Serum ALT, AST, alkaline phosphatase, GGT, and total bilirubin will be monitored in all subjects every 28 (± 2) days throughout the study.
PFTs will be performed at all visits. The QOL instruments will be administered at all visits during the first 336 days (48 weeks) of the study and then every other visit thereafter.

Intervention

During the titration period, subjects will receive 5 mg ambrisentan or placebo once daily for 14 days. Subjects will then receive 10 mg ambrisentan or placebo from the beginning of the treatment period through the remainder of the study.

Study burden and risks

Patients will be subject to the following procedures:
Questionnaires, physical exam, vital signs, HRCT scan, pulmonary function tests, ECG, walk test, blood sampling, biopsy (possibly) and rightheartcatheterisation. Patients who are sexually active should use 2 reliable contraception methods. Patients will be informed regarding this in the informed consent form.

The following adverse events have been included in the informed consent form: Headache, peripheral edema (swelling of the legs and feet), fluid retention (swelling all over the body or unexplained weight gain), nasal congestion (stuffy nose), inflamed nasal passages, red and sore throat and nose, flushing, palpitations (fast or irregular heart beats) (extra heart beats), abdominal pain, shortness of breath, constipation, and anemia (decreases in red blood cells), serious birth defects, possible liver injury and possible lower sperm count in men.

The risks of the study procedures that will be performed are local pain and lightheadedness with blood draws, pain, collapsed lung, infection, bleeding, hematoma, clotting around the catheter, air entering through the catheter, heart rhythm abnormalities, low bloodpressure and rupture of the pulmonary artery with rightheartcatherisation; exposure to radiation with HRCT-scan.

Contacts

Public
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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. Male or females from 40 to 80 years of age
2. Diagnosis of Idiopathic Pulmonary Fibrosis (IPF) based on the following criteria in accordance with ATS-ERS guidelines for diagnosing IPF:
* Definite or probable UIP confirmed on SLB by core pathologist
or
* In absence of SLB, HRCT scan showing definite findings for IPF (bibasilar reticular abnormalities with minimal ground glass opacities) as determined by core review
and three of the following *minor criteria*:
* Age > 50 years
* Insidious onset of otherwise unexplained dyspnea on exertion
* Duration of illness >= 3 months
* Bibasilar, inspiratory crackles
Within 90 days of study enrollment, diagnosis must be confirmed by HRCT
3. Honeycombing <= 5% as assessed on HRCT; HRCT results will undergo a core review process (Section 7.4) to confirm diagnosis.
4. Willingness to undergo RHC at baseline and at Visit 7 or end of study (EOS)
5. Willingness and ability to comply with required monitoring of liver function every 28 days. LFTs include serum ALT, AST, alkaline phosphatase, gamma glutamyl transferase (GGT), and

total bilirubin concentrations

Exclusion criteria

1. 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, chronic use of N-acetylcysteine (prescribed for IPF)
2. Chronic treatment with immunosuppressive, cytotoxic, or antifibrotic drugs including pirfenidone, D penicillamine, colchicine, TNF α antagonists, imatinib, interferon gamma, cyclophosphamide, cyclosporine A, or azathioprine within 30 days of randomization (Section 5.4)
3. Obstructive lung disease as determined by evidence of airflow obstruction on HRCT or physiologic criteria including:
• FEV1/FVC ratio < 0.7
• RV > 120% by plethysmography or significant (verified by radiologist) emphysema on HRCT if plethysmography not available
• Evidence of reactive airway disease by change in FEV1 of > 12% following bronchodilator challenge
4. Active or recent (<= 60 days prior to enrollment) pulmonary or upper respiratory tract infection
5. Hospitalization within 60 days of screening for an acute exacerbation of IPF
(AE IPF)
6. Chronic heart failure (NYHA class III/IV) or known left ventricular ejection fraction <25%
7. Acute or chronic impairment (other than dyspnea) which limits the ability to comply with study requirements and procedures including the 6 min-walk test.

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:	Will not start
Start date (anticipated):	01-02-2009
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ambrisentan
Generic name:	(+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid

Ethics review

Approved WMO Date:	06-02-2009
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	04-06-2009
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	12-08-2009
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	12-05-2010
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

Approved WMO

Date:	04-06-2010
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	09-09-2010
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	21-09-2010
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	EUCTR2008-004405-34-NL
ClinicalTrials.gov	NCT00768300
CCMO	NL25906.099.09

Study results

Summary results
Trial ended prematurely