A Phase 2 Trial to Evaluate the Efficacy of PRM-151 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Published: 08-12-2014
Last updated: 21-04-2024

To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, pooling subjects on a stable dose of pirfenidone or nintedanib and subjects not on other treatment for IPF.

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

Summary

ID

NL-OMON43714

Source
ToetsingOnline

Brief title
PRM-151-202

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
IPF, lung fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Promedior, Inc
Source(s) of monetary or material Support: Promedior Inc.

Intervention

Keyword: Idiopathic Pulmonary Fibrosis (IPF), Pentatraxin-2 protein (PTX-2), Pulmonary Diseases

Outcome measures

Primary outcome

The primary endpoint is the mean change in FVC % predicted from Baseline to

Week 28.

Secondary outcome

* Structural Imaging:

* Mean change from Baseline to Week 28 in total lung volume and volume of

parenchymal features on HRCT (in ml and % of total lung volume) representative

of interstitial lung abnormalities (ILA) including ground glass density,

reticular changes, and honeycombing, using quantitative imaging software.

* Mean change from Baseline to Week 28 in volume of parenchymal features on

HRCT (in ml and % of total lung volume) representative of normal lung

(non-ILA), including normal and mild low attenuation areas, using quantitative

imaging software.

* Correlation between mean change from Baseline to Week 28 in FVC % predicted

and mean change from Baseline to Week 28 in total lung volume and volume of

parenchymal features on HRCT (in ml and % of total lung volume) representative

of interstitial lung abnormalities (ILA), including ground glass density,

reticular changes, and honeycombing by quantitative imaging software.

* Safety: Tolerability/safety will be assessed over the 28 week study period by

the following parameters:

* Incidence of AEs.

* Incidence of serious adverse events (SAEs).

* Incidence of respiratory AEs and SAEs.

* Proportion of subjects discontinuing study drug due to AEs.

* Change from Baseline in hematology and serum chemistries.

* All cause mortality.

* Mortality due to respiratory deterioration.

* Disease related events associated with mortality: The number of *respiratory decline* events over the 28 week study period as defined below:

* Unscheduled visits to a healthcare professional for respiratory status deterioration.

* Urgent care visit for respiratory status deterioration.

* Hospitalization due to a worsening or exacerbation of respiratory symptoms.

All *respiratory decline* events will be further characterized according to the definitions of IPF related acute exacerbation, as proposed by an expert committee sponsored by the IPF Clinical Research Network and the National Heart Lung and Blood Institute (NHLBI) (Collard, Moore et al. 2007) and applied by (Collard, Yow et al. 2013)

* Acute onset of symptoms (< 30 days in duration)

* New radiographic abnormalities (bilateral ground glass or consolidation on HRCT with no pneumothorax or pleural effusion)

* The absence of an identified infectious etiology by routine clinical practice

* Exclusion of alternative causes by routine clinical practice, including:

a. Left heart failure

b. Pulmonary embolism

c. Identifiable cause of acute lung injury

* Pulmonary Function Tests

* Proportion (%) of subjects with a decline in FVC% predicted of * 5% and * 10% from Baseline to Week 28.

* Proportion (%) of subjects with a decline in FVC in ml of * 100 ml and * 200 ml from Baseline to Week 28.

* Proportion of subjects with an increase in FVC % predicted of * 5% and * 10% from Baseline to Week 28.

* Proportion of subjects with an increase in FVC in ml of *100 ml and * 200 ml from Baseline to Week 28.

* Proportion of subjects with stable disease by FVC %, defined as a change in FVC % predicted of <5% from Baseline to Week 28.

* Proportion of subjects with stable disease by FVC in ml, defined as a change in FVC of < 100ml from Baseline to Week 28.

* Mean change from Baseline to Week 28 in % predicted diffusion capacity of carbon monoxide (DLCO).

* Change in 6-minute walk distance, in meters, from Baseline to Week 28.

Study description

Background summary

A double blinded, randomised, placebo controlled Phase 2 Trial to Evaluate the Efficacy of PRM-151 in Subjects with Idiopathic Pulmonary Fibrosis (IPF). The objective is to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, pooling subjects on a

stable dose of pirfenidone or nintedanib and subjects not on other treatment for IPF.

Study objective

To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, pooling subjects on a stable dose of pirfenidone or nintedanib and subjects not on other treatment for IPF.

Study design

This study is a Phase 2, randomized, double-blind, placebo controlled, pilot study designed to evaluate the efficacy and safety of PRM 151 administered through Week 24 to subjects with IPF. Subjects meeting the eligibility criteria for the study will be randomized with a 2:1 ratio to PRM-151 at a dose of 10 mg/kg every 4 weeks or placebo. The randomization will be stratified according to other treatments for IPF (patients receiving pirfenidone or nintedanib and patients with no other treatment for IPF, with a minimum of 25% of patients on no other treatment). Efficacy will be evaluated through pulmonary function tests (PFTs) including spirometry, Diffusion Capacity (DLco) and Total Lung Capacity by Nitrogen washout method, quantitative imaging analysis of high resolution CT (HRCT), 6 minute walk test (6MWT), and patient reported outcomes (PROs).
Subjects will be evaluated for study eligibility during Screening within 4 weeks before enrollment and Baseline assessments. Subjects who are determined to be eligible, based on Screening assessments, will be enrolled in the study and randomly allocated to treatment with PRM 151 or placebo. Subjects will receive study drug treatment for at least 24 weeks.
Approximately 117 subjects will be randomly assigned on a 2:1 basis to treatment with PRM 151 or placebo, as follows:
* PRM 151 10 mg/kg IV infusion over 60 minutes days 1, 3, and 5, then one infusion every 4 weeks
* Placebo IV infusion over 60 minutes on days 1, 3, and 5, then one infusion every 4 weeks

After completing 24 weeks of treatment, subjects may continue with PRM-151 dosing in the open label extension in the absence of disease progression or toxicity warranting discontinuation of therapy.
All subjects will receive PRM-151 10 mg/kg IV Days 1, 3, 5 then every 4 weeks in the extension. Dosing on days 1, 3 and 5 will be repeated every 28 weeks during the extension. PROs, PFTs, spirometry and 6MWT will be done every 4 weeks for the first 24 weeks and then every 12 weeks. DLco, FRC &TLC by nitrogen washout method will be done every 12 weeks. HRCT will be done at 1.5 years (Week 76) and 2.5 years (Week 128) on the same day as DLco and FRC & TLC by nitrogen washout. Subjects are allowed to begin treatment with, or restart treatment with, pirfenidone or nintedanib after the week 28 end of study

assessments have been performed.

Intervention

After the subject decided to participate in the trial, the patient will be randomized to either PRM-151 or placebo, both administered by intravenous infusion for 9 treatments in a period of 24 weeks.

With (almost) every visit all subjects need to complete 2 questionnaires. Next to that physical examination, 6 Minutes walk test, pulmonary function test and blood tests need to be done. next to that, at baseline and at 28 weeks a HRCT is planned.

Study burden and risks

See protocol section 1.5. Risk/Benefit Assessment:
PRM 151, a recombinant form of an endogenous human protein, has been well tolerated in preclinical toxicology studies and Phase 1 and 2 clinical studies, and has shown an early trend towards efficacy in subjects with IPF. Based on encouraging Phase 1 data in subjects with IPF, PRM 151 has the potential to be a safe, disease modifying treatment for a broad spectrum of fibrotic diseases, including IPF.
PRM 151 represents the recombinant version of an endogenous human serum protein, and as such was predicted to have a very favorable safety index. This prediction has been confirmed in multiple preclinical and clinical studies to date. Two Phase 1 studies of PRM 151 administered IV to normal volunteers and IPF subjects have been completed, with no SAEs reported and no other safety signals seen. The single ascending dose study (PRM151A-11EU) tested dose levels as high as 20 mg/kg. The multiple ascending dose study (PRM151F-12GL) demonstrated that PRM 151 administered by 30 minute IV infusion on Days 1, 3, 5, 8 and 15 at up to 10 mg/kg was safe and well tolerated in subjects with IPF, with no SAEs noted in 57 days; similar types and number of TEAEs were reported in both PRM 151 and placebo treated subjects. Safety data from 27 patients with MF, including 24 weeks of safety data in 20 subjects and an additional 12 weeks of safety data in 10, confirms the excellent safety profile of PRM-151 to date. Most adverse events have been Grade 1 or 2 and unrelated to PRM-151, and 5 possibly related SAEs, including one death, have been reported in a group of older patients (median age 67 years) with a serious, life threatening disease.
Risks associated with PRM 151 are inherent in its being the recombinant form of a naturally occurring human protein, and consist of potential development of anti-drug antibodies and infusion reactions. PRM 151 has an endogenous counterpart, and, therefore, anti-drug antibodies could develop that could potentially affect the efficacy of PRM 151 treatments in addition to having the potential to cross-react with endogenous hPTX-2. Anti-drug antibodies were detected in 3 subjects in the MF trial, with no apparent impact on pharmacokinetics, safety, or efficacy. Two subjects had mild infusion

reactions which were easily managed and prevented in the one subject that was rechallenged; anti-drug antibody was detected in one of them.
PRM 151 is not a general immunosuppressant, and treatment with PRM 151 is not expected to increase rates of infection or adversely affect wound healing.
As with any protein therapeutic, the potential for reactions exists and safety procedures will be implemented including careful monitoring of subjects during infusions and of infusion sites. Appropriate personnel, medication, and other requirements for the treatment of potential infusion reactions will be required by the protocol.
PRM 151 is an investigational agent. Subjects are not anticipated to derive direct benefit from participation in studies; the potential benefits of PRM 151 as a therapy for IPF remain to be proven in clinical efficacy studies.

Contacts

Public
Promedior, Inc

Hartwell Ave 101
Lexington MA 02421
US
Scientific
Promedior, Inc

Hartwell Ave 101
Lexington MA 02421
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is aged 40-80 years.
2. Subject has IPF satisfying the ATS/ERS/JRS/ALAT diagnostic criteria (Raghu, Collard et al. 2011).
In the absence of a surgical lung biopsy, HRCT must be *consistent with UIP* defined as meeting either criteria A, B, and C, or criteria A and C, or criteria B and C below:
A. Definite honeycomb lung destruction with basal and peripheral predominance.
B. Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis, with basal and peripheral predominance.
C. Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern.
3. If on pirfenidone or nintedanib, subject must have been on a stable dose of pirfenidone or nintedanib for at least 3 months prior to screening without increase in FVC% predicted on two consecutive PFTs, including screening PFTs. Subjects may not be on both pirfenidone and nintedanib.
4. If not currently receiving pirfenidone or nintedanib, subject must have been off pirfenidone or nintedanib for * 4 weeks before baseline.
5. Subject has a FVC * 50% and * 90% of predicted.
6. Subject has a DLCO * 25% and * 90% of predicted.
7. Minimum distance on 6MWT of 150 meters, with or without supplemental oxygen
8. Subject has a forced expiratory volume in 1 second (FEV1)/FVC ratio > 0.70.
9. Women of child bearing potential (WCBP), defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if * 55 years or 12 months if > 55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use adequate methods of birth control throughout the study. Adequate methods of contraception include use of oral contraceptives or Depo-Provera, with an additional barrier method (diaphragm with spermicidal gel or condoms with spermicide), double-barrier methods (diaphragm with spermicidal gel and condoms with spermicide), partner vasectomy, and total abstinence (only if total abstinence is the preferred method and usual lifestyle of the subject).
10. Subject has a life expectancy of at least 9 months
11. Subject, according to the investigator*s best judgment, can comply with the requirements of the protocol.
12. Subject and the treating physician considered all medicinal treatment options and/or possibly a lung transplantation prior to considering participation in the study. If the subject is on a lung transplant list, the Investigator anticipates the subject will be able to complete the study prior to transplant.
13. Subject has provided written informed consent to participate in the study.

Exclusion criteria

1. Subject has emphysema * 50% on HRCT or the extent of emphysema is greater than the extent of fibrosis according to the reported results of the most recent HRCT.

2. Subject has a history of cigarette smoking within the previous 3 months.
3. Subject has received investigational therapy for IPF within 4 weeks before baseline.
4. Subject is receiving systemic corticosteroids equivalent to prednisone > 10 mg/day or equivalent within 2 weeks of baseline.
5. Subjects received Immuno-suppressants (e.g. methotrexate, azathioprine, cyclophosphamide, cyclosporine, everolimus or other immunosuppressants including those used after organ transplant) are prohibited within 4 weeks of baseline and during the study.
6. Subject has a history of a malignancy within the previous 5 years, with the exception of basal cell skin neoplasms. In addition, a malignant diagnosis or condition first occurring prior to 5 years must be considered cured, inactive, and not under current treatment.
7. Subject has any concurrent condition other than IPF that, in the Investigator*s opinion, is unstable and/or would impact the likelihood of survival for the study duration or the subject*s ability to complete the study as designed, or may influence any of the safety or efficacy assessments included in the study.
8. Subject has baseline resting oxygen saturation of < 89% on room air or with supplemental oxygen.
9. Subjects that are unable to refrain from use of the following:
a. Short acting bronchodilators on the day of and within 12 hours of pulmonary function, DLco, and 6 minute walk assessments.
b. Long acting bronchodilators on the day of and within 24 hours of these assessments.
10. Subject has a known post bronchodilator (short acting beta agonist [SABA] * albuterol or salbutamol) increase in FEV1 of >10% and in FVC of >7.5%.

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:	Recruitment stopped
Start date (anticipated):	07-09-2015

Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PRM-151
Generic name:	recombinant human pentatraxin-2

Ethics review

Approved WMO Date:	08-12-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-05-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-07-2016

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2019
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	EUCTR2014-004782-24-NL
ClinicalTrials.gov	NCT02550873
CCMO	NL51502.078.14