A phase III open-label extension study to evaluate long-term safety and efficacy of PRM-151 in patients with Idiopathic Pulmonary Fibrosis (IPF)

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Study WA42294 is a Phase III open-label extension (OLE) study to assess the long-term safety, efficacy, and pharmacokinetics of PRM-151 in patients with IPF with or without concurrent treatment with pirfenidone or nintedanib. Patients with IPF who...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON52289

Source
ToetsingOnline

Brief title
WA42294/STARSCAPE-OLE

Condition

- Pulmonary vascular disorders

Synonym
cryptogenic fibrosing alveolitis; idiopathic diffuse interstitial pulmonary fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche

Source(s) of monetary or material Support: F. Hoffmann-La Roche Ltd

Intervention

Keyword: extension study, long-term, open-label, phase III

Outcome measures

Primary outcome

This study will evaluate the long-term safety, efficacy and pharmacokinetics of open label PRM 151 in patients with idiopathic pulmonary fibrosis (IPF).

Specific objectives and corresponding endpoints for the study are outlined below.

The safety objective for this study is to confirm the long term safety and tolerability of 10 mg/kg of PRM 151 administered every 4 weeks (Q4W) via intravenous (IV) infusion plus standard of care (SOC) treatment, on the basis of the following endpoints:

• Incidence and severity of all adverse events (AEs), with severity determined according to the 5 point severity scale (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI CTCAE, v.5.0])

• Incidence and severity of infusion related reactions (IRRs) and other AEs of special interest

• Proportion of patients permanently discontinuing study treatment due to AEs

• Change from baseline of targeted clinical laboratory test results

The efficacy objectives are to assess the long term efficacy of 10 mg/kg PRM 151 plus SOC (excluding lung transplantation) administered Q4W via IV infusion

on the basis of the following endpoints:

• Annual rate of decline in forced vital capacity (FVC [mL])

• Annual rate of change in 6 minute walk distance (6MWD)

• Annual rate of decline in FVC% predicted

• Progression free survival, defined as time to first occurrence of *10% absolute decline in % predicted FVC, *15% relative decline in 6MWD, or death

• Change from baseline in University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ)

• Change from baseline in St. George Respiratory Questionnaire (SGRQ) Total Score

• Change from baseline in carbon monoxide diffusing capacity (DLCO)

• Survival, as measured by all cause mortality

Secondary outcome

Exploratory analyses may also be performed for additional measures and subgroups of interest including concurrent use of IPF treatment and geographic region. Details of all such analyses will be provided in the Statistical Analysis Plan (SAP).

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to characterize pharmacokinetics of PRM 151 in patients with IPF (from Cohort A only), on the basis of the following endpoint:

• Serum concentrations of PRM 151 at specified timepoints

The exploratory PK objectives are to evaluate the potential relationship

between drug exposure and the efficacy and safety of PRM 151 on the basis of the following endpoints:

• Relationship between PK for PRM 151 and efficacy endpoints

• Relationship between PK for PRM 151 and safety endpoints

The immunogenicity objective for this study is to evaluate the immune response to PRM 151 in patients with IPF (from Cohort A only) on the basis of the following:

• Prevalence of ADAs at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following:

• Relationship between ADA status and efficacy, safety, or PK endpoints

The exploratory biomarker objective for this study (from Cohort A only) is to identify and/or evaluate biomarkers that can provide evidence of PRM 151 activity and the duration of that activity (i.e., pharmacodynamic biomarkers), are associated with acquired resistance to PRM 151, are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

• Relationship between biomarkers in blood and efficacy, safety, PK,

immunogenicity, or other biomarker endpoints.

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with PRM 151 plus SOC on the basis of the following endpoint:

• Annual rate of change in EuroQol 5 Dimension, 5 Level Questionnaire (EQ 5D 5L) index based, and visual analog scale (VAS) scores

added by protocol v.3:

Two objectives based on PRO assessments were moved from efficacy section to exploratory section because of the unblinded nature of the administration of PRM 151 in this extension study. Two additional exploratory objectives were added to highlight the noteworthiness of these objectives (Section 2.3).

Serious adverse events has been added to list of the criteria based on which safety analyses for this study will be performed (Section 6.3).

* Language has been updated to include efficacy analysis, additional healthcare utilization for respiratory events analysis, and exploratory analysis to reflect suggestions from regulatory agencies and to improve clarity of the text (Sections 6.4 and 6.41).

added by protocol v3:

Annual rate of change in DLCO and IPF-related mortality and respiratory-related mortality are added as an efficacy objective to better align with the rest of the protocol. This was missed in the previous version of the protocol.

Additional changes have been done in the efficacy objectives for improved

clarity (Section 2.2).

Study description

Background summary

Idiopathic pulmonary fibrosis is a specific form of a chronic-fibrosing interstitial pneumonia limited to the lung. It is a progressive inflammatory lung disease that leads to significant morbidity and mortality. Pentraxin-2 (PTX-2) is a highly conserved endogenous serum protein and a soluble pattern recognition receptor (PRR) of the innate immune system that regulates monocyte activation and differentiation. PRM-151 is a recombinant human pentraxin-2 (rhPTX-2) protein. Of importance, patients with IPF (in comparison to healthy subjects) have both increased fibrocyte numbers in circulation and decreased levels of circulating PTX-2.
Supplementing endogenous PTX-2 levels through intravenous administration of PRM-151 should theoretically increase the regulatory capacity of PTX-2 in circulation and at the site of disease, thereby promoting healing and reducing fibrosis.
Robust nonclinical and clinical data exist to support the investigation of PRM-151 in the treatment of fibrotic diseases. Efficacy and safety of PRM-151 is also being investigated in patients with myelofibrosis in a Phase II study. (see Protocol, section 1. background)

Study objective

Study WA42294 is a Phase III open-label extension (OLE) study to assess the long-term safety, efficacy, and pharmacokinetics of PRM-151 in patients with IPF with or without concurrent treatment with pirfenidone or nintedanib. Patients with IPF who have already completed the Phase II 28-week placebo-controlled period (PRM-151-202) and taken part in the OLE (Cohort A); or completed the Phase III Study WA42293 will be eligible to enroll in this study (Cohort B). Additionally, patients who have discontinued treatment or completed the Phase III Study WA42293, and do not wish to receive open-label PRM-151 in this study will be followed-up for survival (Cohort C). No safety or efficacy assessments will be required for these patients. This open-label design will allow an examination of the impact of longer treatment duration on safety, durability of response in lung function, exercise tolerance, and patient reported outcomes as well as pharmacokinetics of PRM-151. (See Protocol, section 1.3.)

Study design

This OLE study is being conducted to confirm the long term safety, efficacy, and pharmacokinetics of PRM 151 in the treatment of eligible patients with IPF who have taken part in Study PRM 151 202 and received the open label study drug (Cohort A) or completed the Phase III Study WA42293 (Cohort B) with PRM 151. Additionally, patients who have discontinued treatment from or have completed Study WA42293 and do not want to receive open label PRM 151 in this study, will be invited to enroll in survival follow up Cohort C. Patients in Cohort C will not receive any treatment and will not undergo any safety or efficacy assessments during the study. Patients who discontinue treatment from Cohorts A and B will automatically transition to Cohort C for long term follow up, unless they withdraw consent from the study.
Approximately 600-700 patients are expected to enroll in the study. Patients will initially receive loading doses of either PRM 151 10 mg/kg IV infusion and/or placebo over 50*70 minutes on Days 1, 3, and 5, then one infusion of PRM 151 Q4W until the end of the study. Patients previously on the placebo arm of Study WA42293 will receive PRM 151 in all three loading doses, whereas patients previously on the active treatment arm of Study WA42293 will receive PRM 151 for the first dose, followed by placebo doses at the 2nd and 3rd loading dose visit. The 2nd and 3rd loading doses will be blinded for Cohort B, to ensure that the blind in Study WA42293 is maintained for patients, site staff, and the Sponsor.

Intervention

Patients will receive IV infusions of 10 mg/kg PRM 151 over approximately 50*70 minutes, with dose based on the patient*s weight recorded at each visit (for loading or reloading doses, weight taken at the clinic visit for the first dose can be applied to the 2nd and 3rd doses).
The non-investigational medicinal products (NIMP) for this study are pirfenidone and nintedanib. The NIMPs are considered background therapy for those patients already receiving either product when entering the study, and rescue therapy for any patient who commences treatment with either product during the study.

added/updated by protocol v3;
* Urinalysis collection has been updated from every 24 weeks to every 12 weeks to align with the collection of urine for optional biomarker sampling (Appendix 1).
* It has been clarified that study completion visit is not required for patients in Cohort C (Appendix 2).

Study burden and risks

PRM 151, a recombinant form of an endogenous human protein, was generally well tolerated in nonclinical toxicity studies and in Phase I and II clinical studies. Clinically and statistically significant positive effects with PRM 151

were observed in the Phase II IPF Study PRM 151 202, both for change in FVC (% predicted) and 6MWD through 28 weeks of treatment. Based on encouraging Phase I and II data in patients with IPF, PRM 151 has the potential to be a well tolerated, disease modifying treatment for a broad spectrum of fibrotic diseases, including IPF.
In the two Phase I studies of PRM-151 administered intravenously to normal volunteers and patients with IPF, no serious adverse events were reported and no other safety signals were 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 serious adverse events noted in 57 days.
As with any protein therapeutic, the potential for reactions exists and safety procedures will be implemented, including careful monitoring of patients 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 and the potential benefits of PRM 151 as a therapy for IPF remain to be proven in clinical efficacy studies. (see Protocol, section 1.3.1)

Contacts

Public
Hoffmann-La Roche

Grenzacherstrasse 124
Basel 4070
CH
Scientific
Hoffmann-La Roche

Grenzacherstrasse 124
Basel 4070
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Patients must meet the following criteria for study entry:
* Signed Informed Consent Form
* In the opinion of the Principle Investigator, participation in the study is in the best
interest of the patient
* Ability to comply with the requirements of the study protocol, according to the
investigator*s best judgment
* Taken part in a previous study of PRM-151, as follows:
o Participated in Study PRM-151-202 (completed the 28-week placebo-controlled period and entered the OLE), and tolerated the study drug in the opinion of the investigator (Cohort A) OR
o Completed study treatment in Study WA42293 (Cohort B) OR
o Participated in Study WA42293 but have discontinued from study treatment (Cohort C; patients who completed treatment in Study WA42293, but no longer wish to take PRM-151 may also join Cohort C)
* For women of childbearing potential: agreement to remain abstinent (refrain from
heterosexual intercourse) or use contraception, as defined below:
Women must remain abstinent or use contraceptive methods with a failure rate of *1% per year during the treatment period and for 8 weeks after the final dose of PRM-151.
A woman is considered to be of childbearing potential if she is postmenarchal, has
not reached a postmenopausal state (*12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to
surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as
determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
Examples of contraceptive methods with a failure rate of *1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit
ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

Hormonal contraceptive methods must be supplemented by a barrier method. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
* For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below: With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 8 weeks after the final dose of PRM-151 to avoid exposing the embryo. Men must refrain from donating sperm during this same period. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:
* Received any experimental treatment other than PRM-151 within 4 weeks or five half-lives of the experimental drug, whichever is longer, prior to the first dose in the OLE study
* Receiving strong inhibitor or inducer of CYP1A2 in patients taking pirfenidone
* Receiving potent inhibitor or inducer of P-gp in patients taking nintedanib
* Acute respiratory or systemic bacterial, viral, or fungal infection at the first visit of the OLE, or within 2 weeks of the first visit for patients joining Cohort A (from

Study PRM-151-202)
* History of smoking (including cigarette, cannabis, cigar, pipe, and vaping) within
3 months prior to the first visit in the OLE
* History of alcohol or substance use disorder within 2 years prior to the first visit of
the OLE or known or suspected active alcohol or substance-use disorder.
* History of severe allergic reaction or anaphylactic reaction to PRM-151
* Clinically significant abnormality on ECG during eligibility assessment that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient.
* Prolonged corrected QT interval > 450 ms (for men) or > 470 ms (for women) based on the Fridericia correction formula.
* Clinically significant laboratory test abnormalities (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient.
* Any of the following laboratory abnormalities known at the time of the first visit
- ALT and/or AST *2.5*upper limit of normal (ULN)
- Total bilirubin *2*ULN
* Pregnant or breastfeeding, or intending to become pregnant during the study (for Cohort A or B patients)

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-12-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Recombinant human pentraxin-2 (PRM-151)
Generic name:	-

Ethics review

Approved WMO Date:	01-02-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-05-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-09-2022
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	EUCTR2020-001429-30-NL
ClinicalTrials.gov	NCT04594707
CCMO	NL75035.078.21