Official Title: A Phase III Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of PRM-151 in Patients With Idiopathic Pulmonary Fibrosis

NCT Number: NCT04552899

Document Dates: Protocol Version 5: 28-April-2022

PROTOCOL

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PROTOCOL NUMBER:	WA42293 (also known as PRM-151-303)
VERSION NUMBER:	5
EUDRACT NUMBER:	2020-000791-38
IND NUMBER:	110,774
NCT NUMBER:	NCT04552899
TEST PRODUCT:	Recombinant human pentraxin-2 (rhPTX-2; PRM-151); *Zinpentraxin Alfa*
MEDICAL MONITOR:	[redacted], M.B.B.S.
SPONSOR NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL DATE:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
5	See electronic date stamp on the final page.	—	—	—
3	13 November 2020	Japan	4	27 July 2021
2	29 June 2020	VHP	2	12 November 2020
1	13 March 2020	—	—	—

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol WA42293 has been amended to incorporate the changes made to address feedback from health authorities during review of clinical trial applications along with additional changes initiated by the Sponsor. Changes to the protocol, along with a rationale for each change, are summarized below.

The following changes were made based on recommendations from the Japan Pharmaceuticals and Medical Devices Agency and were implemented in Protocol WA42293, Version 4 (Japan):

- The exclusion criterion for women who are pregnant or breastfeeding, and women of childbearing potential has been added (Sections 4.1.2 and 5.5.3.1). The inclusion criteria (Section 4.1.1) have been updated to reflect the above change.
- Serum and urine pregnancy tests for women of childbearing potential have been removed from sample collection and schedule of assessments sections (Section 4.5.12).
- An appendix has been added to clarify the additional pharmacokinetic samples that will be collected for some patients enrolling in Japan (Appendix 4).

The following additional changes have been made to Protocol WA42293, Version 5:

- Text has been added to describe galectin-1 and galectin-3 host cell protein identified within first generation PRM-151 drug product. It has been further clarified that an additional purification step will be applied to the second generation PRM-151 which will not contain detectable levels of Chinese hamster ovary cell galectins (Sections 1.2 and 4.3.1.1).
- Text has been added to describe the sugar galactose-α-1,3-galactose identified in first and second generation PRM-151 drug product and on the increased risk of anaphylaxis or hypersensitivity reaction in patients with a history of tick bites, red meat allergy, or IgE antibodies directed against galactose-α-1,3-galactose (Sections 1.2.2 and 5.1.2).
- Text has been added on the potential risk of post-implantation fetal loss associated with PRM-151 (Sections 5.1 and 5.1.3)
- Text has been added to address assessment of risks related to SARS-CoV-2 infection (Section 1.3.1).
- Text has been updated to clarify how assessments from patients who received lung transplant will be analyzed (Section 2.1.1).
- “Progression-free survival” has been updated to “Time to disease progression” in secondary efficacy objective as per United States Food and Drug Administration (FDA) suggestion to better reflect the nature of the endpoint (Section 2.1.2).
- Text has been updated to clarify that safety analyses may also be performed for subgroups of interest and details of all such analyses will be provided in the Statistical Analysis Plan (Section 2.2).

- Text has been updated to clarify that all sites in Hong Kong and Taiwan can contribute to the China cohort regardless of their National Medical Products Administration accreditation status (Sections 3.1.1, 4.1, 4.1.1, 4.2.1, 6, and 6.12).
- The exclusion criterion regarding “clinically significant abnormality on electrocardiogram or laboratory tests during eligibility assessment” has been split into two different criteria for clarity (Section 4.1.2.).
- Testing requirement for tuberculosis has been clarified in the exclusion criteria (Section 4.1.2).
- Text has been updated to clarify measuring samples for longitudinal endogenous PTX-2 levels in order to evaluate if there is any modulation after rhPTX-2 drug is administered (Section 4.2.2).
- It has been clarified that at dosing visits, vital signs should be measured predose (within 60 minutes prior to dosing), every 15 minutes during the infusion, and 30−60 minutes postdose (Section 4.3.2.1).
- It has been clarified that all past anti fibrotic therapy will be recorded in the Prior and Concurrent Anti-fibrotic Use form and all COVID-19 vaccines received will be recorded on the Concomitant Medications eCRF (Sections 4.4 and 4.5.3).
- Text has been added to include approved vaccination including COVID-19 vaccine as a permitted therapy (Section 4.4.1)
- Text has been added to include high-dose corticosteroids (equivalent to prednisone $>$10 mg daily) as a prohibited therapy unless it is clinically indicated (Section 4.4.2)
- Text has been added to include post-infusion lab samples that are required to be collected after infusion of drug (Section 4.5.2).
- Table 2, Sequence of Assessments, has been updated to clarify the break between assessment of diffusing capacity for carbon monoxide (DL_{CO}) and 6-Minute Walk Test (Sections 4.5.2 and 4.5.7).
- It has been clarified that patients who had high-resolution computed tomography (HRCT) at screening, will have further HRCT imaging at Week 52 (Section 4.5.2).
- Text has been added to include family history of Idiopathic pulmonary fibrosis (IPF) to gather comprehensive understanding of medical history of patients with IPF (Section 4.5.3).
- Text has been added to include tuberculosis as a respiratory infection to gather comprehensive understanding of medical history of patients (Section 4.5.3).
- It has been clarified that medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditioned eCRF (Section 4.5.3 and 5.4.1).
- It has been clarified that DL_{CO} assessment will be performed using local equipment and only data from acceptable over-read spirometry and DL_{CO} maneuvers will be used for eligibility confirmation and data analysis (Section 4.5.6).
- Wording has been added to clarify that the oxygen titration procedure should be conducted as per local standard of care (Section 4.5.7).

- It has been clarified that a blood sample for a serum tryptase sample and complement C3 test should be collected at the time of a suspected anaphylaxis or hypersensitivity event whenever possible, and at the first follow-up visit after the event to reflect the management guidelines and to help determine whether tryptase and complement C3 levels were elevated during the event (Sections 4.5.12, 5.1.3, and Appendix 1).
- Additional information has been provided on sample collection to align with infusion-related reaction management guidelines (Table 2) included in the protocol (Sections 4.5.12, 5.1.3, and Appendix 1).
- Text has been added to include optional urine sample collection at different timepoints (Section 4.5.16.3).
- Text has been added to clarify the difference between study treatment discontinuation and study discontinuation. Additionally, it is expected that if a patient discontinues from treatment, they should continue with study visits and assessments (Section 4.6).
- Text has been added for better understanding of potential risk associated with PRM-151 (Section 5.1).
- Text has been updated in “Abnormal Liver Function Tests” to align with the updated Hy’s law calculation (Section 5.4.5.7).
- Text has been updated to clarify that patients diagnosed with idiopathic pulmonary fibrosis are the target patient population for this study (Section 6.1).
- As per FDA request, assessments following hospitalization for COVID-19 will be collected and analysed, given the likelihood of COVID hospitalization will continue for appreciable time (Section 6.1).
- As per the request by FDA, the supplementary estimand has been removed since its handling of intercurrent events is not clinically relevant (Section 6.1).
- Text has been deleted since the statement is no longer considered relevant to drug compliance with respect to this study (Section 6.4).
- Language has been updated in primary efficacy analysis, sensitivity and supplementary analyses of primary and key secondary endpoints (previous section), and analyses addressing the effect of missing data to reflect suggestions from regulatory agencies, and to improve clarity of the text (Sections 6.4 and 6.41).
- Text has been updated to clarify the interim analyses planned for this study (Section 6.11).
- It has been clarified that an external global Steering Committee will provide oversight of Studies WA42293 and WA42294 (Section 9.5).
- International non-proprietary name has replaced the RO number throughout the protocol and has also been added in the footer of each page.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PRM-151 IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS**
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MEDICAL MONITOR:	[redacted], M.B.B.S.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____
Principal Investigator's Name (print)

_____ _____
Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PRM-151 IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS**
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PHASE:	Phase III
INDICATION:	Idiopathic pulmonary fibrosis
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of PRM-151 compared with placebo in patients with idiopathic pulmonary fibrosis (IPF). Specific objectives and corresponding endpoints for the study are outlined below.

EFFICACY OBJECTIVES

Primary Efficacy Objective

The primary efficacy objective is to demonstrate superiority of 10 mg/kg PRM-151 plus standard of care treatment as needed (excluding lung transplantation) administered every 4 weeks (Q4W) via intravenous (IV) infusion, over matching placebo plus standard of care treatment as needed (excluding lung transplantation), on lung function on the basis of the following endpoint:

- Absolute change from baseline to Week 52 in forced vital capacity (FVC [mL])

The primary comparison will be made regardless of whether patients changed or withdrew from randomized treatment or changed additional treatment (excluding lung transplantation) during the study. Patients who received a lung *transplant* will be assessed as if *a lung transplant* had *not been available during the* study*, and all assessments after the transplant will not be included in the analysis.*

Secondary Efficacy Objective

The secondary efficacy objective is to demonstrate superiority of 10 mg/kg PRM-151 plus standard of care treatment as needed (excluding lung transplantation) administered Q4W via IV infusion, over matching placebo plus standard of care treatment as needed (excluding lung transplantation) on the basis of the following endpoints:

- Absolute change from baseline to Week 52 in 6-minute walk distance (6MWD) *(in meters)*
- Absolute change from baseline to Week 52 in FVC% predicted
- *Time to disease progression*, defined as time to first occurrence of ≥ 10% absolute decline in % predicted FVC, ≥ 15% relative decline in 6MWD, or death

- Time to first respiratory-related hospitalizations (defined as non-elective hospitalizations due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF, as determined by *the Clinical* Adjudication Committee)
- Change from baseline to Week 52 in University of California, San Diego–Shortness of Breath Questionnaire (UCSD-SOBQ)
- Change from baseline to Week 52 in St. George Respiratory Questionnaire (SGRQ) Total Score
- Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF, as determined by *the Clinical* Adjudication Committee
- Change from baseline to Week 52 in carbon monoxide diffusing capacity (DLCO)
- Survival, as measured by all-cause mortality

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of PRM-151 plus standard of care treatment as needed (excluding lung transplantation) compared with matching placebo plus standard of care treatment as needed (excluding lung transplantation) on the basis of the following endpoints:

- Change from baseline to Week 52 in FVC% predicted, FVC (mL), by concurrent therapy stratum (i.e., with nintedanib treatment vs. with pirfenidone treatment vs. without pirfenidone or nintedanib treatment)
- Change from baseline to Week 52 in FVC% predicted, FVC (mL), by MUC5B *risk allele positive or negative* status
- Change from baseline to Week 52 in 6MWD, by concurrent therapy stratum (i.e., with nintedanib treatment vs. with pirfenidone treatment vs. without pirfenidone or nintedanib treatment)
- Change from baseline to Week 52 in SGRQ Individual Domains (Symptoms, Activity, and Impacts) Score
- Change from baseline to Week 52 in the 6-minute walk test (6MWT) pre-test to pre-test measurements of Borg dyspnea score, fatigue score, and oxygen saturation
- Change from baseline to Week 52 in the 6MWT pre-test to post-test measurements of Borg dyspnea score, fatigue score, and oxygen saturation
- Change from baseline to week 52 in the 6MWT post-test to post-test measurements of Borg dyspnea score, fatigue score, and oxygen saturation
- Change from baseline to Week 52 in quantitative imaging analysis parameters of HRCT scan of the thorax
- Length of hospital stay for respiratory-related hospitalizations, total time in intensive care units due to respiratory causes, deaths due to respiratory causes, and unscheduled outpatient clinic/urgent care/emergency room utilization related to respiratory events
- A decline or an increase in FVC% predicted of $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ from baseline to Week 52
- A decline or an increase in FVC in mL of ≥ 100 mL and ≥ 200 mL from baseline to Week 52
- A decline or an increase in 6MWD $\geq 5\%$, $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ from baseline to Week 52
- A decline or an increase in 6MWD ≥ 25 m, and 50 m from baseline to Week 52
- Number of acute exacerbations during the 52 weeks
- At least one acute exacerbation during the 52 weeks; as determined by *the Clinical* Adjudication Committee
- Survival as measured by IPF-related mortality
- Survival as measured by respiratory-related mortality

- Disease progression defined as: ≥10% absolute decline in % predicted FVC; respiratory hospitalization; or a decline of 50 m in 6MWD
- Disease progression and subsequently start pirfenidone or nintedanib or switch from nintedanib to pirfenidone (or vice versa)
- Time to worsening on the UCSD-SOBQ, as indicated by a change in score of 10 points or greater
- Time to worsening on the SGRQ total score, as indicated by a change in score of 7 or greater
- Time to worsening on the SGRQ Activity domain, as indicated by a change in score of 5 or greater
- Time to worsening on the SGRQ Symptom Domain, as indicated by a change in score of 8 or greater
- Time to worsening on the SGRQ Impact Domain, as indicated by a change in score of 7 or greater
- Change in pulmonary function test (PFT) parameters (FVC, 6MWT, or DLCO) from baseline to Week 52 between SARS-CoV-2 antibody positive compared with negative patients
- Change in PFT parameters (FVC, 6MWT, or DLCO) from baseline to Week 52 in patients who develop SARS-CoV-2 antibodies during treatment (not present at baseline)

Efficacy evaluations will be performed for the primary, secondary, and exploratory efficacy endpoints as detailed in the protocol. Exploratory analyses may also be performed for additional measures and subgroups of interest. Details of all such analyses will be provided in the Statistical Analysis Plan (SAP).

SAFETY OBJECTIVE

The safety objective for this study is to confirm the safety and tolerability of 10 mg/kg of PRM-151 administered Q4W via IV infusion plus standard of care treatment as needed relative to matching placebo plus standard of care treatment as needed in a population of all dosed patients, on the basis of the following endpoints:

- Incidence and severity of adverse events, 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 IRRs and other adverse events of special interest
- Proportion of patients permanently discontinuing study treatment due to adverse events
- Change from baseline in targeted clinical laboratory test results

Safety analyses may also be performed for subgroups of interest. Details of such analyses will be provided in the SAP.

PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize pharmacokinetics of PRM-151 in patients with IPF on the basis of the following:

- Plasma 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:

- Relationship between PK for PRM-151 and efficacy endpoints
- Relationship between PK for PRM-151 and safety endpoints

IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to PRM-151 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

BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to PRM-151 (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to PRM-151, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of PRM-151 activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following:

- Relationship between biomarkers in blood listed in Section 4.5.12 and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with PRM-151 plus standard of care treatment as needed on the basis of the following endpoint:

- Change from baseline to Week 52 in EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based, and visual analog scale (VAS) scores

STUDY DESIGN

DESCRIPTION OF STUDY

This Phase III, randomized, double-blind, placebo-controlled, pivotal study is designed to confirm the efficacy and safety of PRM-151 in the treatment of patients with IPF during a 52-week period. At the end of this 52-week period, patients will be invited to enroll in an open-label extension (OLE) study (Study WA42294) to receive treatment with PRM-151. Patients who do not enroll in the OLE study will be followed up for an additional 4 weeks (to Week 56, for safety monitoring).

The OLE study will provide patients with further study assessments and PRM-151 treatment on an ongoing basis. However, the OLE study will also consist of a long-term survival cohort, where patients who do not want further study assessments or treatment can enroll (for long-term collection of survival data only).

Patients meeting the eligibility criteria for the study will be randomized to PRM-151 10 mg/kg Q4W or placebo. Efficacy will be evaluated through assessment of functional capacity as measured by FVC, 6MWD, other pulmonary function tests (PFTs), and assessment of patients with respiratory events leading to hospitalizations, progression of disease, acute IPF exacerbations.

Patient reported outcomes (PROs) will be assessed using the SGRQ, UCSD-SOBQ, and EQ-5D-5L.

Dyspnea, fatigue, and SpO_2 will be assessed based on measurements taken during the 6MWT. For patients who require a HRCT scan during the screening period, an additional chest HRCT scan will be performed at Week 52. Patients who do not require a HRCT scan during the screening period (i.e., they already have a historic HRCT scan of acceptable quality performed within 12 months prior to screening) will not be required to perform a scan at Week 52.

Treated patients will be followed until the end of the 52-week study period unless the patient withdraws consent for follow-up or dies.

Patients will be evaluated for study eligibility during a screening period of up to 4 weeks. If any patient is prevented from completing required screening procedures within the 4-week period due to unforeseeable circumstances. Screening may be extended up to a maximum of 2 weeks. Patients who are determined to be eligible based on the screening assessments will be randomized into the study and randomly allocated to treatment with PRM-151 or placebo.

Patients entering the screening period on anti-fibrotic therapy (pirfenidone or nintedanib) should have been on treatment for at least 3 months, and on a stable dose for at least 4 weeks prior to the screening visit and are expected to remain on their specific dose and regimen throughout the study duration unless dose reduction or discontinuation is indicated for safety or tolerability reasons.

Patients entering the screening period of the study NOT on anti-fibrotic treatment (pirfenidone or nintedanib), either treatment naive or having previously taken and discontinued, must have been off such treatment for at least 4 weeks prior to the screening visit and during screening. At the time of consent, if a patient is considering starting treatment with either nintedanib or pirfenidone, the patient should be advised of being on treatment for at least 3 months prior to screening.

For all patients receiving anti-fibrotic therapy, the investigator should document the dose, frequency, and duration of the anti-fibrotic drug. For patients not receiving anti-fibrotic therapy during the screening period, the investigator should document the reason(s).

During the study, patients may initiate pirfenidone or nintedanib as rescue, if determined to be clinically indicated by the investigator. The investigator may consider discussing changes in anti-fibrotic therapy with the Medical Monitor throughout the study. The investigator is required to document the specific reason for introducing anti-fibrotic therapy in patients who were randomized into the study not on anti-fibrotic therapy.

Approximately 658 patients will be randomly assigned on a 1:1 basis to treatment with PRM-151 or placebo, as follows:

- PRM-151 Group: PRM-151 10 mg/kg IV infusion over 50–70 minutes on Days 1, 3, and 5, then one infusion Q4W for 48 weeks
- Placebo Group: Matched placebo IV infusion over 50–70 minutes on Days 1, 3, and 5, then one infusion Q4W for 48 weeks

The randomization will be stratified as follows:

- Concurrent use of nintedanib treatment versus pirfenidone treatment versus no concurrent treatment
- Region: China (including Hong Kong and Taiwan), North America (United States and Canada), Europe (including eastern Europe), Latin America, and Rest of World (including east Asia, Australia, and New Zealand)

All patients will have a final assessment visit at Week 52 (4 weeks after the final study drug infusion). Patients will be invited to enroll in an OLE study at this point (Study WA42294), and if they roll over into that study, the Week 52 visit will be considered their end of study visit. Patients who do not enroll in the OLE study will have their end of study visit at Week 56, in addition to the Week 52 visit.

This study will enroll approximately 658 patients globally across all sites. Enrollment will be globally competitive. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase at sites in mainland China, Hong Kong, and Taiwan The global population will include all patients enrolled during the global enrollment phase and the China subpopulation will include all patients enrolled *in China, Hong Kong and Taiwan* (i.e., during both the global enrollment phase and the extended China enrollment phase).

Individuals who do not meet the criteria for participation in this study (screen failure) may be eligible for rescreening once for selected reasons. In addition, the screening period may be extended if a patient fails a test due to technical issues with the test and the patient will be allowed to repeat the test (e.g., lab sample hemolyzed and not able to be analyzed).

NUMBER OF PATIENTS

Approximately 658 patients with IPF will be enrolled during the global enrollment phase of this study. After completion of the global enrollment phase, additional patients may be enrolled *in China, Hong Kong, and Taiwan* in an extended China enrollment phase to ensure a total enrollment that is sufficient to support registration in China Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 40–85 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the requirements of the study protocol, according to the investigator's best judgment
- Documented diagnosis of IPF per the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline
- HRCT pattern consistent with the diagnosis of IPF, confirmed by central review of chest HRCT (available HRCT of acceptable quality performed within 12 months prior to screening or obtained during the screening period) and central review of lung biopsy (LB), if available
- Minimum 6MWD of 150 meters with maximum use of 6 L/min at sea-level and up-to 8 L/min at altitude (≥5000 feet [1524 meters] above sea level) of supplemental oxygen while maintaining oxygen saturation of ≥83% during the 6MWT during screening
- FVC ≥45% predicted during screening *as determined by the over-reader*
- Forced expiratory volume in 1 second (FEV_1)/FVC ratio >0.70 during screening *as determined by the over-reader*
- DLCO ≥30% and ≤90% of predicted during screening (Hgb corrected or uncorrected) *as determined by the over-reader*
- If receiving pirfenidone or nintedanib treatment for IPF, the patient must have been on treatment for at least 3 months and on a stable dose for at least 4 weeks prior to screening, and during screening (with no contraindications according to local prescribing information)
- If not currently receiving nintedanib or pirfenidone treatment (either treatment naïve or having previously taken and discontinued) must have discontinued such treatment ≥4 weeks prior to screening and during screening

  If patient is considering starting treatment with either nintedanib or pirfenidone, patient must be on treatment for at least 3 months prior to screening, provided there are no contraindications according to local prescribing information.
- For women of childbearing potential *(excluding patients enrolling in Japan)*: 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.
- Anticipated life expectancy of at least 12 months at baseline, according to the investigator's judgment
- Patient and investigator considered all medicinal treatment options and/or possibly lung transplantation prior to considering participation in the study. If the patient is on a lung transplant list, the investigator anticipates the patient will be able to complete the study prior to transplant.
- For patients enrolled in the extended China enrollment phase: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Evidence of other known causes of interstitial lung disease (e.g., domestic and occupational environmental exposures, connective-tissue disease, and drug toxicity)
- FVC% predicted value showing improvement in the 6-month period prior to screening and including screening value, as assessed by the investigator
- Emphysema present on $\geq$50% of the HRCT, or the extent of emphysema is greater than the extent of fibrosis, according to central review of the HRCT
- Receiving nintedanib in combination with pirfenidone
- Received cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agents (including but not limited to methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine or other steroid sparing agent) within 4 weeks *prior to or during screening* screening
- Receiving systemic corticosteroids equivalent to prednisone $>$10 mg/day or equivalent within 2 weeks prior to *or during* screening
- 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 either during screening or prior to screening and not successfully resolved 4 weeks prior to screening visit
- *Positive* interferon gamma release assay test *for tuberculosis during screening*: Patients who have completed treatment for tuberculosis within 6 months prior to screening, and have no evidence of recurrent disease do not need to be tested.
- Resting oxygen saturation of $<$ 89% using up to 4 L/min of supplemental oxygen at sea level and up-to 6 L/min at altitude ($\geq$ 5000 feet [1524 meters] above sea level) during screening
- Co-existing acute or chronic medical condition that, in the investigator's opinion, would substantially limit the ability to comply with study requirements or may influence any of the safety or efficacy assessments included in the study
- Class IV New York Heart Association chronic heart failure
- Historical evidence of left ventricular ejection fraction $<$35%

- Presence of pulmonary hypertension that, in the investigator's opinion, would substantially limit the ability to comply with study requirements or may influence any of the safety or efficacy assessments included in the study
- Cardiopulmonary rehabilitation program based on exercise training that has been completed within 8 weeks prior to screening or planned to start during the patient's enrollment in this trial
- History of smoking (including cigarette, cannabis, cigar, pipe and vaping) within 3 months prior to *or during* screening
- History of alcohol or substance use disorder within 2 years prior to *or during* screening or known or suspected active alcohol or substance-use disorder
- History of a malignancy within the 5 years prior to screening, with the exception of basal cell or squamous cell skin neoplasms. In addition, a malignant diagnosis or condition that occurred more than 5 years prior to screening, and any basal cell or squamous cell neoplasm must be considered cured, inactive, and not under treatment.
- Unable to refrain from use of the following:
  - Short acting bronchodilators (SABA) within 4 hours before pulmonary function, DLCO, and 6MWT assessments
  - Once daily, long-acting bronchodilators within 24 hours before pulmonary function, DLCO, and 6MWT assessments
  - Twice daily, long-acting bronchodilators within 12 hours before pulmonary function testing, DLCO, and 6MWT assessments
- Known post-bronchodilator response in FEV_1 and/or FVC $\geq$ 12% and $\geq$ 200 mL, respectively
- Receipt of an investigational drug within 4 weeks, or 5 half-lives, whichever is longer, prior to *or during* screening
- Previous treatment with PRM-151
- History of severe allergic reaction or anaphylactic reaction to a biologic *agent*<u>*including any allergies to the additives of the drug product.*</u>
- Clinically significant abnormality on ECG during screening *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) *on ECG during screening,* based on the Fridericia correction formula
- *Clinically significant* laboratory *test abnormalities during screening* (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 during screening:
  - ALT and/or AST $\geq$ 2.5 $\times$ upper limit of normal (ULN)
  - Total bilirubin $\geq$ 2 $\times$ ULN
- Pregnant or breastfeeding, or become pregnant during the study or within 8 weeks after the final dose of PRM-151

  Women of childbearing potential must have a negative serum pregnancy test result within 30 days prior to initiation of study drug.
- *Women of childbearing potential (Only for patients enrolling in Japan)*
  - *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).*

END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs (i.e., last patient in the global and extended China enrollment phases combined) or the date at which the last data point required for statistical analysis (i.e., Week 52 efficacy assessments) or safety follow-up is received from the last patient (global and extended China enrollment phases combined), whichever occurs later. The end of the study is expected to occur 56 weeks after the last patient is enrolled.

LENGTH OF STUDY

The total length of the study is approximately 2.5 years.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal product (IMP) for this study is PRM-151. Placebo is also considered an IMP in this study.

TEST PRODUCT (INVESTIGATIONAL DRUG)

Patients randomized to study drug will receive IV infusions of 10 mg/kg PRM-151 over 50 to 70 minutes, with dose based on the patient's weight taken at the same clinic visit (for loading or reloading doses, the weight taken at the first clinic visit for the first dose can be applied to the second and third doses).

COMPARATOR

Patients randomized to placebo will receive IV infusions of placebo over 50–70 minutes.

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

The non-investigational medicinal products (NIMPs) for this study are pirfenidone and nintedanib. The NIMPs are considered background therapy for those patients already receiving either product when entering the trial and rescue therapy for any patient who commences treatment with either product during the trial.

STATISTICAL METHODS

Unless otherwise specified, all baseline and efficacy analyses will be based on the full analysis set (FAS) defined as all randomized subjects who received at least one administration (full or partial dose) of study drug and will use the grouping as assigned by randomization. The safety evaluable population will include all randomized patients who received at least one administration (full or partial dose) of study drug and will be grouped by treatment received.

The primary analysis will occur when the last enrolled patient has completed the Week 52 study visit. Significance testing of the primary and secondary endpoints will account for multiplicity and control family-wise type I error, which is fixed at 0.05 two-sided. The study has one single primary efficacy endpoint (absolute change from baseline to Week 52 in FVC [mL]) and one family of secondary efficacy endpoints that have been ordered in a prespecified sequence, starting with the key secondary endpoint, absolute change from baseline to Week 52 in 6MWD. The planned statistical analysis will control the overall type I error for the testing of these efficacy endpoints by applying a fixed-sequence statistical strategy, testing all the endpoints according to the pre-specified order. All hypothesis tests will be two-sided unless otherwise specified.

The global population will include all patients enrolled during the global enrollment phase , and the China subpopulation will include all patients enrolled *in China, Hong Kong and Taiwan* (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subpopulation.

PRIMARY ANALYSIS

The primary estimand will evaluate the effectiveness of PRM-151 plus standard of care treatment as needed (excluding lung transplantation) versus matching placebo plus standard of care treatment as needed (excluding lung transplantation). It corresponds to the difference in outcome attributable to the randomized study drug, whatever changes in the treatment regimen (randomized drug and any associated treatment) occurs afterwards (excluding lung transplantation), as described in Mallinckrodt et al. 2017 and Mallinckrodt et al. 2012. Lung transplantation will be handled as a particular intercurrent event (see below). The attributes of the estimand are as follows:

- The treatment regimen of interest is study drug (PRM-151 or placebo) as randomized, in combination with any background or additional treatment (i.e., PRM-151 or placebo taken alone or as an add-on to standard of care with pirfenidone or nintedanib, dosed as required) including all changes in standard of care treatment and all other additional treatments, with the exclusion of lung transplantation.
- The population is *patients diagnosed with idiopathic pulmonary fibrosis* as defined through the inclusion/exclusion criteria presented in Section 4.1 of the protocol. All patients randomized having received at least one administration (full or partial dose) of the study drug (all treated patients) will be included in the analysis (FAS).
- The variable is the absolute change from baseline to Week 52 in FVC mL for the primary efficacy endpoint.
- The population-level summary measure is the between randomized treatments difference in mean change from baseline *at* Week 52 in FVC mL.
- Intercurrent events (post-randomization events):

  Any change in initial treatment regimen (change in study drug, change in standard of care, use of prohibited medication) will be considered irrelevant in defining the treatment effect of interest. As the primary objective is to assess the effectiveness of PRM-151, the analysis will be performed ignoring any such intercurrent event.

  Deaths are expected to be infrequent as the study plans to include patients with a life expectancy longer than the study duration. Assessments following death will be assigned with values to designate treatment failure. Further details will be provided in the SAP.

  Lung transplantation: Lung transplantation is expected to be rare during the study, as patients likely to receive a lung transplantation during the study are excluded. Any data recorded after lung transplantation will be censored from the analysis because they are no longer an accurate measure of efficacy reflecting the diseased lung(s). In some instances, FVC can improve to over 80% following lung transplantation or even 100% for bilateral lung transplantation 6–12 months after surgery.

The primary efficacy analysis will be performed on the FAS population. All FVC mL measurements that meet the minimal level of quality will be used for this analysis, except those recorded after lung transplantation, whatever other intercurrent events might have occurred before that were recorded. Assessments following death will be assigned with values to designate treatment failure, and the details will be provided in the SAP.

The comparison of PRM-151 with placebo will be carried out via a two-sided statistical test. The primary efficacy endpoint will be analyzed using a linear mixed-effect model with random intercept and random slope, with FVC mL measured at each timepoint as *the* dependent variable, stratification factors, age, sex, height, and treatment by time interaction as fixed effects, and subject and time as random effects. The random intercept represents deviations from the mean baseline FVC mL measure for each subject. The model will assume an unstructured covariance structure. If there are convergence problems with the model, the following covariance structures will be tested: compound symmetry, first-order autoregressive [AR(1)] and Toeplitz. The covariance structure converging to the best fit, based on Akaike's information criterion (AIC), will be used. The comparison of PRM-151 with placebo will be carried out by computing the estimate of the difference in absolute change from baseline at Week 52 between the two treatment arms with 95% CIs and p-value.

DETERMINATION OF SAMPLE SIZE

The purpose of this study is hypothesis testing regarding the effect of PRM-151 versus placebo.

With the planned sample size of 658 patients, the study has a power of 0.89 using a two-sided type I error level of 0.05 to detect a standardized effect-size of 0.25 on change from baseline to Week 52 in FVC mL.

Optional Interim Analyses

No *other* efficacy interim analyses are planned at this time. However, in exceptional circumstances, when patient enrollment and study conduct is significantly impacted by external factors such that study completion does not seem feasible (e.g., ongoing or worsening impact of the global COVID-19 pandemic, the availability of compelling clinical trial results for an external

competitor molecule, or significant changes in standard of care), the Sponsor may choose to conduct one interim efficacy analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim *efficacy* analysis is conducted, the Sponsor will remain blinded. The interim *efficacy* analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter. If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWD	6-minute walk distance
6MWT	6-minute walk test
ADA	anti-drug antibody
ALAT	Latin American Thoracic Society
ATS	American Thoracic Society
AUC	area under the plasma concentration-time curve
CHO	*Chinese Hamster Ovary Cell*
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DAMP	damage-associated molecular patterns
DLCO	diffusing capacity for carbon monoxide
EC	Ethics Committee
ECM	extracellular matrix
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
ERS	European Respiratory Society
FAS	full analysis set
FcγR	Fcγ receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HCP	*Host cell protein*
hPTX-2	human pentraxin-2
HRCT	high-resolution computed tomography
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee

Abbreviation	Definition
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IL-10	interleukin-10
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INN	*International Nonproprietary Name*
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
JRS	Japanese Respiratory Society
LB	lung biopsy
LS	least squares
MAD	multiple ascending dose
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NGS	next-generation sequencing
NIMP	non-investigational medicinal product
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PFT	pulmonary function test
PK	pharmacokinetic
PRO	patient-reported outcome
PRR	pattern recognition receptor
PTX-2	Pentraxin-2
Q4W	every 4 weeks
RBR	Research Biosample Repository
rhPTX-2	recombinant human pentraxin-2
SAD	single ascending dose
SAP	Statistical Analysis Plan
SGRQ	St. George Respiratory Questionnaire
SOC	standard of care
TEDE	Total Effective Dose Equivalent
UCSD-SOBQ	University of California, San Diego-Shortness of Breath Questionnaire

Abbreviation	Definition
UIP	usual interstitial pneumonia
ULN	upper limit of normal
VAS	visual analog scale
WES	whole exome sequencing
WGS	whole genome sequencing
w/v	weight/volume

1. BACKGROUND

1.1 IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is a rare, specific form of chronic, fibrosing, interstitial pneumonia limited to the lung and leads to an irreversible loss of lung function. It has the histopathologic pattern of usual interstitial pneumonia (UIP) upon analysis of a surgical lung biopsy. Historically, patients who received a diagnosis of IPF required a surgical lung biopsy; however, the current definition allows for an IPF diagnosis through clinical and radiological methods. The diagnosis of IPF requires the exclusion of other known causes of interstitial lung disease (ILD), such as domestic and occupational environmental exposures, connective-tissue disease, and drug toxicity (Raghu et al. 2011). Patient prognosis is poor with the 5-year survival rate for IPF previously reported as being between 20% and 40% (Olson et al. 2007). In 2015, the incidence of IPF in North America and Europe was estimated at 3 to 9 cases per 100,000 person-years, with lower incidence in Asia and South America (Hutchinson et al. 2015). Although rare, the incidence of IPF is increasing, likely due to an increasing recognition of the disease and the recent development of uniform diagnostic criteria (Raghu et al. 2018). IPF disproportionately affects men over the age of 60 (Raghu et al. 2018).

Pirfenidone and nintedanib are currently the only pharmacologic therapies approved for the treatment of IPF (Raghu et al. 2015). The rate of decline in forced vital capacity (FVC) is slower in patients treated with pirfenidone and nintedanib. However, neither treatment halts disease progression or improves any objective measurements of disease status (Nathan et al. 2016). Therefore, disease progression and respiratory decline is inevitable. Thus, a need for additional novel treatment approaches remains.

Evidence suggests that epithelial damage and abnormal wound repair contribute to the pathogenesis of IPF (Richeldi et al. 2017). Fibrocytes, usually inactive fibroblast-like cells derived from peripheral blood monocytes, have been implicated in this process (De Biasi et al. 2015). A loss of control of the mechanisms halting the normal wound healing process leads to persistence of inflammatory cells (particularly monocyte-derived cell populations such as macrophages and fibrocytes), elevated levels of cytokines, chemokines, growth factors, and other signaling molecules, excessive deposition of collagen types 1 and 3, and inhibition of enzymes that degrade extracellular matrix (ECM) proteins (Lupher and Gallatin 2006).

Over time, continuing insults result in progressive lung fibrosis (pathologic accumulation of excessive ECM) and increasingly compromised lung function due to thickening/stiffening of the interstitium. In established disease, pulmonary function tests (PFTs) identify restrictive disease (reduced total lung capacity) and abnormal gas exchange (reduced carbon monoxide diffusion) (Raghu et al. 2011). Signs and symptoms that develop over time include exertional dyspnea and cough as well as fatigue, weight loss, myalgia, and clubbing of the fingers and toes (Richeldi et al. 2017).

IPF is estimated to be the primary cause of death due to respiratory failure in 60% of patients with IPF and acute exacerbations of the disease are associated with a particularly high risk of respiratory failure (Frankel and Schwarz 2009). Other common causes of death include acute coronary syndromes, congestive heart failure, lung cancer, infection, and venous thromboembolic disease (Frankel and Schwarz 2009).

1.2 PRM-151

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 (Steel and Whitehead 1994; Gewurz et al. 1995; Pepys et al. 1997; Garlanda et al. 2005; Mantovani et al. 2008).

Recent discoveries about the biology of tissue repair and fibrosis have elucidated the important role that PTX-2 plays biologically in regulating processes that relate to scar prevention and healing. PTX-2 is an agonist that binds to Fcγ receptors (FcγRs) on monocytes and promotes their differentiation into regulatory macrophages, which function to promote epithelial healing and resolution of inflammation and scarring. PTX-2 also prevents the differentiation of monocytes into M2 pro-fibrotic macrophages and fibrocytes, preventing the formation of fibrosis. During normal homeostasis, PTX-2 serves as a naturally circulating regulatory protein that specifically binds to apoptotic or necrotic debris in circulation and rapidly removes it through FcγR-mediated phagocytosis by monocytes and macrophages within the spleen and liver. This process suppresses a systemic innate activation response to those damage-associated molecular pattern (DAMP) signals (Cox et al. 2014).

PRM-151 is a recombinant human pentraxin-2 (rhPTX-2) protein. It is produced via Chinese hamster ovary cell culture, purified and formulated as a sterile liquid for intravenous (IV infusion. Like the native human protein, PRM-151 is expressed and purified as a non-covalent, homo-pentamer. Each monomer in the pentamer exhibits the same 204 amino acid primary sequence. The theoretical average molecular weight of the fully glycosylated, bi-sialylated monomers in each pentamer is 25462.5 Da. The theoretical average molecular weight of the corresponding pentamer is 127,313 Da.

PRM-151 mediates its activity by coupling recognition of DAMPs within injured tissue to specific phagocytosis through FcγR on monocytes. This process both removes the inflammatory and fibrotic stimulation provided by the DAMP signals, and actively stimulates the generation of a regulatory macrophage population identified through increased local expression of interleukin-10 (IL-10).

Of importance, patients with IPF (in comparison to healthy subjects) have both increased fibrocyte numbers in circulation (Moeller et al. 2009) and decreased levels of circulating PTX-2 (Murray et al. 2011).

Supplementing endogenous PTX-2 levels through *IV* 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, summaries of which are provided in the following sections. Efficacy and safety of PRM-151 is also being investigated in patients with myelofibrosis in a Phase II study. For more information on nonclinical or clinical investigations, please refer to the PRM-151 Investigator's Brochure.

1.2.1 *PRM-151 Host Cell Proteins*

Mass spectroscopy analysis of PRM-151 was performed to characterize host cell protein (HCP) impurities, which led to the identification of Chinese hamster ovary cell galectin-1 (CHO Gal-1) and CHO galectin-3 (CHO Gal-3). It was found that CHO Gal-1 and CHO Gal-3 co-purifies with PRM-151, and has been present in Phase 2 and Phase 3 batches of investigational medicinal product (IMP).

The Sponsor performed an assessment of toxicology, safety, and efficacy on the potential impact of the presence of CHO Gal-1/3 in the PRM-151 drug product. Nonclinical toxicity data suggest that the overall risk to patients of direct adverse effects due to CHO Gal-1/3 at levels present in the drug product is low. There continues to be a favorable benefit/risk assessment based on the clinical data from the Phase 2 study to date (which used drug substance that has now been confirmed to have these host cell proteins present at the time). Levels of HCPs in the drug product that are equal to or below the levels identified in batches used to supply the Phase 2 studies, are not anticipated to adversely impact the known benefit/risk profile of PRM-151; there are no new safety risks, and there is no direct evidence of impact on efficacy.

In order to control the CHO Gal-1/3 levels, each batch of PRM-151 will be tested for the two HCPs by mass spectrometry. Only batches with levels equal to or lower than the threshold level will be released for use in clinical studies. An additional purification step will be applied to the 'second generation' drug product and thus it will not contain detectable levels of CHO galectins. Second generation drug will be implemented in 2022.

1.2.2 *Galactose-α-1,3-galactose (a-Gal)*

As part of the extended physicochemical characterization, the analysis of N-linked glycan profiles has shown the presence of galactose-a-1,3-galactose (a-Gal) at low levels in both 1st and 2nd generation PRM-151. The highest level of a-Gal observed was 0.3% in 1st generation batches. For 2nd generation PRM-151, levels <3% of a-Gal have been observed.

The Sponsor conducted an assessment of safety regarding the a-Gal glycan and concluded that PRM-151 containing a-Gal at the levels found is suitable for use in clinical studies with the benefit-risk ratio remaining favorable. More information on the presence of a-Gal is provided in the PRM-151 Investigator's Brochure (IB).

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The current study is a confirmatory, randomized, double-blind, placebo-controlled, Phase III clinical trial to assess the efficacy and safety of PRM-151 in patients with IPF with or without concurrent treatment with pirfenidone or nintedanib.

The primary efficacy endpoint for this study will be the absolute change from baseline to Week 52 in FVC (mL), and the key secondary endpoint will be the absolute change in 6-minute walk distance (6MWD) over the same interval. Results from previous Phase I and Phase II studies have produced robust safety and efficacy data, establishing a PRM-151 dose and treatment regimen, and are strongly supportive of conducting a Phase III study to confirm efficacy and safety. Summary of the Phase I and II study outcomes are as follows:

- In a Phase I study in healthy participants and patients with pulmonary fibrosis, administration of PRM-151 increased circulating pentraxin 2 concentrations 6- to 13-fold (Dillingh et al. 2013).
- An additional Phase I study in patients with IPF showed improvements in predicted percentage of FVC value and 6MWD following treatment with PRM-151 (Van den Blink et al. 2016).

The randomized, placebo-controlled Phase II efficacy and safety Study PRM-151-202 of 10 mg/kg of PRM-151 every 4 weeks (Q4W) in patients with IPF revealed clinically and statistically significant efficacy outcomes and showed an acceptable safety profile in a population of patients predominantly (~80%) receiving standard-of-care anti-fibrotic treatment (Raghu et al. 2018):

- The primary endpoint was change in FVC (% predicted) from baseline to Week 28. This endpoint was successfully met with a between-group difference in least squares (LS) mean change in FVC [% predicted] of + 2.3 in favor of PRM-151 (95% CI: 0.9 to 3.7; p = 0.0014).
- Although the study was not powered for formal hypothesis testing of secondary endpoints, encouraging results were also observed for 6MWD (between-group difference in LS mean change from baseline to Week 28 = 31.3 m [95% CI: 14.7 to 47.8, p = 0.0002]) and FVC (mL) (between-group difference in LS mean change from baseline to Week 28 = 114.6 mL [95% CI: 4.4 to 224.8, p = 0.041]).
- Clinically and statistically meaningful changes observed on the two entirely different prognostic endpoints (FVC [% predicted] and 6MWD) as outlined above suggest that the treatment effect observed for PRM-151 is not due to chance.

- The treatment effect for PRM-151 versus placebo was independent of patients receiving concurrent pirfenidone or nintedanib, or no concurrent therapy for IPF.
- The most common adverse events in the PRM-151 versus placebo group were cough (18% vs. 5%), fatigue (17% vs. 10%), and nasopharyngitis (16% vs. 23%).
- Serious adverse events occurred in 6 patients (7.8%) in the PRM-151 group and 4 patients (10.3%) in the placebo group. None of the serious adverse events were considered related to the study treatment.
- Three patients (2.6%) experienced adverse events that led to discontinuation from the study drug (2 patients in the PRM-151 group and 1 patient in the placebo group). One patient in the placebo group died from pneumonia.

Recently completed analyses of the open-label extension (OLE) of study PRM-151-202 provided additional evidence for the efficacy and safety of 10 mg/kg of PRM-151 administered Q4W (Raghu et al. 2019):

- The reduction in deterioration of FVC and 6MWD have been retained in the group initially randomized to PRM-151, and patients from the placebo group who crossed over to PRM-151 treatment show a reduction in the rate of decline for both FVC and 6MWD upon initiation of active therapy.
- Adverse events were consistent with long-term IPF sequelae. Thirty-one (28%) patients had serious adverse events, mostly unrelated to PRM-151. Those occurring in two or more patients were pneumonia (six [5%] of 111), IPF exacerbation (four [4%]), IPF progression (four [4%]), and chest pain (two [2%]). Twenty-one (19%) patients had severe adverse events, of which IPF exacerbation and IPF progression each occurred in two (2%) patients. Two (2%) patients experienced life-threatening adverse events (one had pneumonia and one had small-cell lung cancer extensive stage).

Overall, these data further support the efficacy and safety of administration of PRM-151 10 mg/kg Q4W in patients with IPF, with or without concurrent use of pirfenidone or nintedanib.

The Sponsor believes these are important findings that merit confirmation in a pivotal program, with the objective of obtaining registration of PRM-151 for the treatment of patients with IPF.

1.3.1 Benefit–Risk Assessment

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, both for change in FVC (% predicted) and 6MWD through 28 weeks of treatment. Based on encouraging Phase I and II data in subjects 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; similar types and number of treatment-emergent adverse events were reported in both PRM-151 and placebo treated subjects.

In the Phase II study (PRM-151-202; n = 116), PRM-151 was generally well tolerated through at least 6 months of treatment as evidenced by the following:

- None of the serious adverse events reported during the study were considered related to the study treatment.
- Treatment-emergent adverse events (serious and non-serious) leading to temporary discontinuation of study treatment were more common in the PRM-151 group than the placebo group overall (six patients [7.8%] and one patient [2.6%], respectively), but these events were distributed across a range of body systems with no single preferred term reported in more than one patient and did not appear to indicate a safety risk for PRM-151.
- The most common adverse event assessed as possibly or probably related to study treatment was fatigue (16 events in nine patients from the PRM-151 group [11.7%] and three events in three patients from the placebo group [7.7%]).
- Adverse events of cough with possible or probable relationship to study treatment were reported in seven patients from the PRM-151 group (9.1%; seven events). No patient from the placebo group was reported with possibly or probably related cough adverse events.
- Four infusion-related reactions (IRRs) occurred in three patients, two patients in the PRM-151 group (2.6%) and one patient in the placebo group (2.6%). One patient in the PRM-151 group experienced dizziness and another experienced a hypertensive crisis event; one patient in the placebo group experienced two hypertensive crisis events. There was no difference between treatment arms in the nature or frequency of IRRs. None of the IRR events was deemed serious. There were no IRR events among the seven patients with anti-drug antibodies (ADAs [six patients in the PRM-151 group; one patient in the placebo group]) through Week 28.

Risks associated with PRM-151 are inherent in it being the recombinant form of a naturally occurring human protein and consist of potential development of ADA and infusion reactions. PRM-151 has an endogenous counterpart; therefore, ADAs 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.

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. Individuals who have chronic medical issues may be at higher risk for serious illness from COVID-19, including those with pulmonary fibrosis. However as stated above, it is not anticipated that PRM-151 will increase the risk of infection with SARS-CoV-2 or the severity of infection. *Based on the mechanism of action of PRM-151, a possible interaction between PRM-151 treatment and COVID-19 vaccination is not expected. For patients enrolling in this study and receiving PRM-151 treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).*

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.

1.3.2 Risks Associated with Radiologic Imaging

The high-resolution computed tomography (HRCT) scans performed for this study will involve the delivery of small amounts of radiation to the patient. The amount of radiation received has a low risk of harmful effects, and evaluation of IPF with HRCT is typical in clinical practice to monitor disease or response to therapy. The protocol's radiation dose is "as low as reasonably achievable" (ALARA) to obtain the quality of images necessary for imaging of lung abnormalities and quantification by image analysis software.

The main potential risk from exposure to radiation is cancer. The relative risk of developing adverse effects from radiation, such as future development of radiation-induced malignancy, is exceedingly small compared to the risk of mortality inherent to IPF. From currently available data, the U.S. Nuclear Regulatory Commission has adopted a risk value for an occupational dose of one rem (0.01 Sieverts) Total Effective Dose Equivalent (TEDE) of approximately one chance in 2,500 of fatal cancer per rem of TEDE received. For this protocol, the dose will vary, depending on the specific HRCT scanner technology available at each site, but the volumetric HRCT dose index is estimated to be less than 10 milliGray with effective dose for a standard patient of less than 3 milliSieverts (0.003 Sieverts) per scan. The dose will be adjusted appropriately to assure consistent image quality, based on patient size. No populations at potentially higher risk for radiation exposure such as young children or pregnant women will be involved in the study.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of PRM-151 compared with placebo in patients with IPF. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective is to demonstrate superiority of 10 mg/kg PRM-151 plus standard of care treatment as needed (excluding lung transplantation) administered Q4W via IV infusion, over matching placebo plus standard of care treatment as needed (excluding lung transplantation), on lung function on the basis of the following endpoint:

- Absolute change from baseline to Week 52 in forced vital capacity (FVC [mL])

The primary comparison will be made regardless of whether patients changed or withdrew from randomized treatment or changed additional treatment (excluding lung transplantation) during the study. Patients who received a lung transplant will be assessed as if *a lung transplant had not been available during the study, and all assessments after the transplant will not be included in the analysis.*

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective is to demonstrate superiority of 10 mg/kg PRM-151 plus standard of care treatment as needed (excluding lung transplantation) administered Q4W via IV infusion, over matching placebo plus standard of care treatment as needed (excluding lung transplantation) on the basis of the following endpoints:

- Absolute change from baseline to Week 52 in 6MWD *(in meters)*
- Absolute change from baseline to Week 52 in FVC% predicted
- *Time to disease progression,* defined as time to first occurrence of ≥ 10% absolute decline in % predicted FVC, ≥ 15% relative decline in 6MWD, or death
- Time to first respiratory-related hospitalizations (defined as non-elective hospitalizations due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF, as determined by *the Clinical* Adjudication Committee)
- Change from baseline to Week 52 in University of California, San Diego–Shortness of Breath Questionnaire (UCSD-SOBQ)
- Change from baseline to Week 52 in St. George Respiratory Questionnaire (SGRQ) Total Score
- Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF, as determined by *the Clinical* Adjudication Committee
- Change from baseline to Week 52 in carbon monoxide diffusing capacity (DLCO)

- Survival, as measured by all-cause mortality

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of PRM-151 plus standard of care treatment as needed (excluding lung transplantation) compared with matching placebo plus standard of care treatment as needed (excluding lung transplantation) on the basis of the following endpoints:

- Change from baseline to Week 52 in FVC% predicted, FVC (mL), by concurrent therapy stratum (i.e., with nintedanib treatment vs. with pirfenidone treatment vs. without pirfenidone or nintedanib treatment)
- Change from baseline to Week 52 in FVC% predicted, FVC (mL), by MUC5B *risk allele positive or negative* status
- Change from baseline to Week 52 in 6MWD, by concurrent therapy stratum (i.e., with nintedanib treatment vs. with pirfenidone treatment vs. without pirfenidone or nintedanib treatment)
- Change from baseline to Week 52 in SGRQ Individual Domains (Symptoms, Activity, and Impacts) Score
- Change from baseline to Week 52 in the 6-minute walk test (6MWT) pre-test to pre-test measurements of Borg dyspnea score, fatigue score, and oxygen saturation
- Change from baseline to Week 52 in the 6MWT pre-test to post-test measurements of Borg dyspnea score, fatigue score, and oxygen saturation
- Change from baseline to Week 52 in the 6MWT post-test to post-test measurements of Borg dyspnea score, fatigue score, and oxygen saturation
- Change from baseline to Week 52 in quantitative imaging analysis parameters of HRCT scan of the thorax
- Length of hospital stay for respiratory-related hospitalizations, total time in intensive care units due to respiratory causes, deaths due to respiratory causes, and unscheduled outpatient clinic/urgent care/emergency room utilization related to respiratory events
- A decline or an increase in FVC% predicted of $\geq$5%, $\geq$10%, and $\geq$15% from baseline to Week 52
- A decline or an increase in FVC in mL of $\geq$100 mL and $\geq$200 mL from baseline to Week 52
- A decline or an increase in 6MWD $\geq$5%, $\geq$10%, $\geq$15%, and $\geq$20% from baseline to Week 52
- A decline or an increase in 6MWD $\geq$25 m, and 50 m from baseline to Week 52
- Number of acute exacerbations during the 52 weeks
- At least one acute exacerbation during the 52 weeks; as determined by *the Clinical* Adjudication Committee

- Survival as measured by IPF-related mortality
- Survival as measured by respiratory-related mortality
- Disease progression defined as: ≥10% absolute decline in % predicted FVC; respiratory hospitalization; or a decline of 50 m in 6MWD
- Disease progression and subsequently start pirfenidone or nintedanib or switch from nintedanib to pirfenidone (or vice versa)
- Time to worsening on the UCSD-SOBQ, as indicated by a change in score of 10 points or greater
- Time to worsening on the SGRQ total score, as indicated by a change in score of 7 or greater
- Time to worsening on the SGRQ Activity domain, as indicated by a change in score of 5 or greater
- Time to worsening on the SGRQ Symptom Domain, as indicated by a change in score of 8 or greater
- Time to worsening on the SGRQ Impact Domain, as indicated by a change in score of 7 or greater
- Change in PFT parameters (FVC, DLCO) or 6MWD from baseline to Week 52 between SARS-CoV-2 antibody positive compared with negative patients
- Change in PFT parameters (FVC, DLCO) or 6MWD from baseline to Week 52 in patients who develop SARS-CoV-2 antibodies during treatment (not present at baseline)

Efficacy evaluations will be performed for the primary, secondary, and exploratory efficacy endpoints as detailed in Section 6.5. Exploratory analyses may also be performed for additional measures and subgroups of interest. Details of all such analyses will be provided in the Statistical Analysis Plan (SAP).

2.2 SAFETY OBJECTIVE

The safety objective for this study is to confirm the safety and tolerability of 10 mg/kg of PRM-151 administered Q4W via IV infusion plus standard of care treatment as needed relative to matching placebo plus standard of care treatment as needed in a population of all dosed patients, on the basis of the following endpoints:

- Incidence and severity of adverse events, 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 IRRs and other adverse events of special interest

- Proportion of patients permanently discontinuing study treatment due to adverse events

  Change from baseline in targeted clinical laboratory test results

Safety evaluations will be performed as detailed in Section 6.5. Safety analyses may also be performed for subgroups of interest. Details of such analyses will be provided in the SAP.

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize pharmacokinetics of PRM-151 in patients with IPF on the basis of the following:

- Plasma 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:

- Relationship between PK for PRM-151 and efficacy endpoints
- Relationship between PK for PRM-151 and safety endpoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to PRM-151 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

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to PRM-151 (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to PRM-151, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of PRM-151 activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following:

- Relationship between biomarkers in blood listed in Section 4.5.12 and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with PRM-151 plus standard of care treatment as needed on the basis of the following endpoint:

- Change from baseline to Week 52 in EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based, and visual analog scale (VAS) scores

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

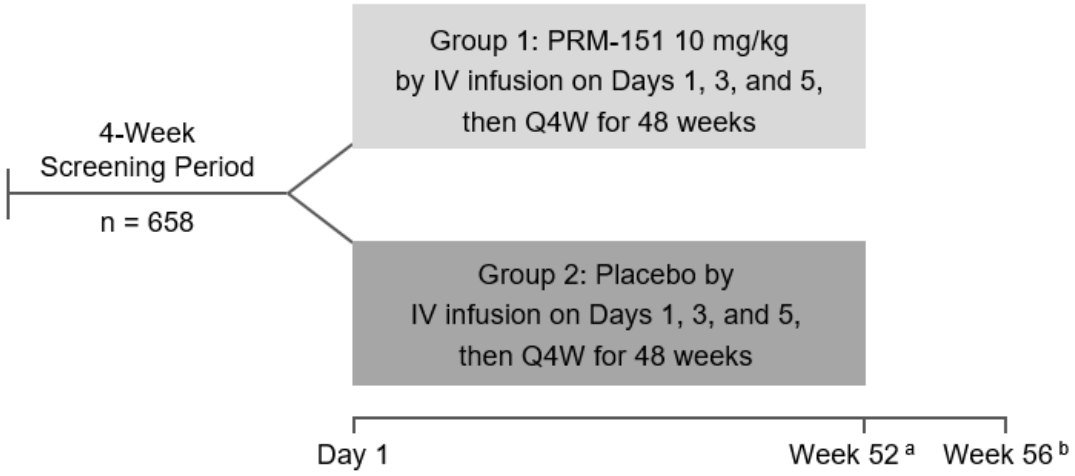
3.1.1 Overall Study Design and Plan

This Phase III, randomized, double-blind, placebo-controlled, pivotal study is designed to confirm the efficacy and safety of PRM-151 in the treatment of patients with IPF during a 52-week period. At the end of this 52-week period, patients will be invited to enroll in an open-label extension study (Study WA42294) to receive treatment with PRM-151. Patients who do not enroll in the OLE study will be followed up for an additional 4 weeks (to Week 56, for safety monitoring).

The OLE study will provide patients with further study assessments and PRM-151 treatment on an ongoing basis. However, the OLE study will also consist of a long-term survival cohort, in which patients who do not want further study assessments or treatment can enroll (for long-term collection of survival data only).

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



OLE = open-label extension; Q4W = once every 4 weeks.

[a] Patients will have a final assessment visit at Week 52 (4 weeks after the final study drug infusion). For patients enrolling in the OLE study, this will also be their end of study visit.

[b] Patients who do not enroll in the OLE study will have their final assessment visit at Week 52, followed by an end of study visit at Week 56 (8 weeks after the final study drug infusion).

Patients meeting the eligibility criteria for the study will be randomized to PRM-151 10 mg/kg Q4W or placebo. Efficacy will be evaluated through assessment of functional capacity as measured by FVC, 6MWD, other PFTs, and assessment of patients with respiratory events leading to hospitalizations, progression of disease, acute IPF exacerbations.

Patient reported outcomes (PROs) will be assessed using the SGRQ, UCSD-SOBQ, and EQ-5D-5L.

Dyspnea, fatigue, and SpO_2 will be assessed based on measurements taken during the 6MWT. For patients who require a HRCT scan during the screening period, an additional chest HRCT scan will be performed at Week 52. Patients who do not require a HRCT scan during the screening period (i.e., they already have a historic HRCT scan of acceptable quality performed within 12 months prior to screening) will not be required to perform a scan at Week 52.

Treated patients will be followed until the end of the 52-week study period unless the patient withdraws consent for follow-up or dies.

Patients will be evaluated for study eligibility during a screening period of up to 4 weeks. If any patient is prevented from completing required screening procedures

within the 4-week period due to unforeseeable circumstances, screening can be extended up to a maximum of 2 weeks. Patients who are determined to be eligible based on the screening assessments will be randomized into the study and randomly allocated to treatment with PRM-151 or placebo.

Patients entering the screening period on anti-fibrotic therapy (pirfenidone or nintedanib) should have been on treatment for at least 3 months, and on a stable dose for at least 4 weeks prior to the screening visit, and are expected to remain on their specific dose and regimen throughout the study duration unless dose reduction or discontinuation is indicated for safety or tolerability reasons.

Patients entering the screening period of the study NOT on anti-fibrotic treatment (pirfenidone or nintedanib), either treatment naive or having previously taken and discontinued, must have been off such treatment for at least 4 weeks prior to the screening visit and during screening. At the time of consent, if a patient is considering starting treatment with either nintedanib or pirfenidone, the patient should be advised of being on treatment for at least 3 months prior to screening (Section 4.1.1).

For all patients receiving anti-fibrotic therapy, the investigator should document the dose, frequency, and duration of the anti-fibrotic drug. For patients not receiving anti-fibrotic therapy during the screening period, the investigator should document the reason(s).

During the study, patients may initiate pirfenidone or nintedanib as rescue, if determined to be clinically indicated by the investigator. The investigator may consider discussing changes in anti-fibrotic therapy with the Medical Monitor throughout the study. The investigator is required to document the specific reason for introducing anti-fibrotic therapy in patients who were randomized into the study not on anti-fibrotic therapy.

Approximately 658 patients will be randomly assigned on a 1:1 basis to treatment with PRM-151 or placebo, as follows:

- PRM-151 Group: PRM-151 10 mg/kg IV infusion over 50–70 minutes on Days 1, 3, and 5, then one infusion Q4W for 48 weeks
- Placebo Group: Matched placebo IV infusion over 50–70 minutes on Days 1, 3, and 5, then one infusion Q4W for 48 weeks

The randomization will be stratified as follows:

- Concurrent use of nintedanib treatment versus pirfenidone treatment versus no concurrent treatment
- Region: China (including Hong Kong and Taiwan), North America (United States and Canada), Europe (including eastern Europe), Latin America, and Rest of World (including east Asia, Australia, and New Zealand)

All patients will have a final assessment visit at Week 52 (4 weeks after the final study drug infusion). Patients will be invited to enroll in an OLE study at this point (Study WA42294), and if they roll over into that study, the Week 52 visit will be considered their end of study visit. Patients who do not enroll in the OLE study will have their end of study visit at Week 56, in addition to the Week 52 visit (see Table 1).

Table 1 Final Assessment and End of Study Visits

	Last Infusion of Study Treatment	Final Assessment Visit	End of Study Visit
Patients enrolling in OLE study for ongoing PRM-151 treatment	Week 48	Week 52	Week 52
Patients enrolling in OLE study for survival follow-up only	Week 48	Week 52	Week 56
Patients not enrolling in OLE study	Week 48	Week 52	Week 56

OLE = open-label extension study (Study WA42294).

This study will enroll approximately 658 patients globally across all sites. Enrollment will be globally competitive. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase at sites in mainland China, Hong Kong, and Taiwan The global population will include all patients enrolled during the global enrollment phase and the China subpopulation will include all patients *enrolled in China, Hong Kong, and Taiwan* (i.e., during both the global enrollment phase and the extended China enrollment phase).

Individuals who do not meet the criteria for participation in this study (screen failure) may be eligible for rescreening once for selected reasons. In addition, the screening period may be extended if a patient fails a test due to technical issues with the test and the patient will be allowed to repeat the test (e.g., lab sample hemolyzed and not able to be analyzed).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs (i.e., last patient in the global and extended China enrollment phases combined) or the date at which the last data point required for statistical analysis (i.e., Week 52 efficacy assessments) or safety follow-up is received from the last patient (global and extended China enrollment phases combined), whichever occurs later. The end of the study is expected to occur 56 weeks after the last patient is enrolled.

The Sponsor may decide to terminate the study at any time.

The total length of the study is approximately 2.5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for PRM-151 Dose and Schedule

Dose selection for this Phase III trial of PRM-151 in IPF is based on prior nonclinical and clinical data demonstrating favorable safety and efficacy at equivalent doses of up to 10 mg/kg IV. In summary:

- Nonclinical studies and in vitro potency assays indicate that the effective dose range in humans is predicted to be 0.2–10 mg/kg IV.
- PRM-151 has demonstrated a decrease in lung fibrosis in preclinical models of IPF (TGF-β1 overexpression, and bleomycin-induced lung fibrosis); the effect lasted for as long as 30 days after dosing (Murray et al. 2011; Murray et al. 2010; Pilling et al. 2007), which supports Q4W dosing.
- The dose of 10 mg/kg IV selected for the current study has a dose-based safety margin of 10x and an area under the plasma concentration-time curve (AUC)-based safety margin of approximately 5x compared to the rat no-observed-adverse-effect-level (NOAEL) of 100 mg/kg from a 26-week repeat-dose Good Laboratory Practice (GLP) compliant toxicity study.
- The dose of 10 mg/kg IV has been identified as an appropriate dose level in patients with IPF based on the outcomes of the single ascending dose (SAD) and multiple ascending dose (MAD) Phase I studies conducted in healthy subjects and patients with IPF (studies PRM151A-11EU [Dillingh et al. 2013], PRM151F-12GL [van den Blink et al. 2016]), and further supported by the randomized Phase II efficacy and safety study PRM-151-202 with PRM-151 (Raghu et al. 2018) and the interim analysis from study PRM-151-202 OLE (Raghu et al. 2019):

  The Phase I MAD study PRM151F-12GL revealed that plasma levels of PRM-151 (C_{max} and AUC; baseline-corrected) were dose proportional across the range of doses from 1 to 10 mg/kg (Dillingh et al. 2013). Additionally, while the study was not designed to support formal hypothesis testing, the mean change from baseline to Day 57 (which was 42 days after administration of last dose of study drug) in the 6MWD trended upward with increasing dose of IV PRM-151 (–11 m, +6 m, and +35 m at 1 mg/kg, 5 mg/kg, and 10 mg/kg, respectively; and declined in the placebo group: –11 m). Similar observations were noted in mean change from baseline in FVC. The effects of PRM-151 were well tolerated at doses up to 10 mg/kg IV by patients with IPF (van den Blink et al. 2016). These preliminary efficacy and safety data in patients with IPF supported further evaluation of 10 mg/kg IV administered Q4W.

  In the randomized, placebo-controlled Phase II efficacy and safety study, PRM-151-202, 10 mg/kg IV of PRM-151 was administered on Days 1, 3, and 5 followed by Q4W administration for 24 weeks in patients with IPF. Data from this study demonstrated clinically and statistically significant efficacy outcomes and showed an acceptable safety profile (Raghu et al. 2018).

Additionally, 52-week data on 111 patients enrolled in the 128-week OLE of study PRM-151-202 have shown durability of effect of PRM-151 at 10 mg/kg Q4W IV in patients randomized to the active arm. Furthermore, patients in the placebo group crossing over to receive PRM-151 (10 mg/kg IV) in the extension phase experienced a reduction in the rate of decline for FVC (% predicted) and FVC (mL) and no decline in 6MWD upon initiation of active therapy (Raghu et al. 2019). Every 28 weeks, patients in this study received PRM-151 on Days 1, 3, and 5.

These data further support the selection of the dose of 10 mg/kg IV PRM-151 Q4W for the confirmatory Phase III study in patients with IPF, with or without concurrent use of pirfenidone or nintedanib.

Loading Dose

Patients with IPF have increased fibrocyte numbers in circulation and decreased levels of circulating PTX-2. PRM-151 mediates its activity by coupling recognition of DAMPs within injured tissue to specific phagocytosis through FcγR on monocytes. Loading doses were instituted in the preclinical models to increase the exposure of PTX-2 in the fibrotic tissue space within the lungs, to increase the likelihood that all local monocyte/macrophage lineage cells would be polarized to the pro-resolutive state.

The Phase I MAD study (PRM151F-12GL) showed that administration of 5–10 mg/kg in humans increased circulating levels of PTX-2 by 5–8 fold. This data suggested that a dosing regimen that includes a loading dose may have persistent positive biologic effects up to 42 days after the last administration.

Loading doses of PRM-151 on Days 1, 3, and 5 were administered in the Phase II study (PRM-151-202) and repeat loading doses were administered in the 128-week OLE (PRM-151-202) every 28 weeks.

Given the duration of this proposed Phase III study (52 weeks), it is expected that there may be occasional dose interruptions. Repeat loading of PRM-151 will be required on the resumption of study treatment (three doses administered on alternate days), if any dose of study drug is missed (see Section 4.3.2.1). This is to ensure adequate tissue exposure of PRM-151, given the estimated tissue half-life of PTX-2 (24–30 days, see PRM-151 Investigator's Brochure for further details).

3.3.2 Rationale for Key Primary and Secondary Endpoints

For the Phase III study, FVC (mL) has been selected as the primary outcome measure based on the common clinical use of this reproducible measure to monitor disease progression and on the results of Phase II study PRM-151-202. Change from baseline in FVC is the most commonly employed primary endpoint in clinical studies assessing treatments for IPF and has been used as the basis of approval for other IPF therapies (Nathan and Meyer 2014; Table of Surrogate Endpoints, FDA, 2018). In addition to the

advantages of being easy to measure and highly reproducible, FVC is considered to be clinically reflective of the burden of the IPF disease process (Nathan and Meyer 2014; Saketkoo et al. 2014). FVC outcomes have been associated with subsequent survival, as declines in FVC have been shown to correlate with increased risk of mortality (Saketkoo et al. 2014; Collard et al. 2003).

The Sponsor has selected 6MWD as the key secondary outcome measure for this study as this test has the combined attributes of providing a direct measure of patients' functional ability as well as having an association with patient outcomes in IPF (Lederer et al. 2006; du Bois et al. 2014; Eaton, et al. 2005; Flaherty, et al. 2006; Caminati et al. 2009; Nathan et al. 2014; Singh, et al. 2014, Brown and Nathan 2017).

The 6MWD is a valid and responsive clinical endpoint, which provides objective and clinically meaningful information regarding functional status and near-term prognosis (Nathan et al. 2015). A difference of 24 to 45 m has been reported as clinically important in the IPF population (du Bois et al. 2011; Nathan et al. 2013; Verma et al. 2011). A change of 14 to 30.5 m has been found to be clinically important across multiple patient groups (Bohannon and Crouch 2016), and the 6MWD was found to be associated with health-related quality of life measures in patients with IPF, representing a meaningful outcome for patients (Verma et al., 2011). Furthermore, a decline of more than 25 m has been independently associated with 1-year all-cause mortality in IPF (Swigris et al. 2010; du Bois et al. 2014; Brown and Nathan 2017). Additionally, the 6MWD has been found to be sufficiently robust to serve as the primary efficacy outcome measure for therapies intended to treat pulmonary arterial hypertension (Galiè et al. 2009).

Data from the PRM-151 Phase II study (Raghu et al. 2018) have demonstrated stabilization of the decline in 6MWD in the group receiving PRM-151 with a placebo-corrected treatment effect of +31.3 m. These data warrant confirmation of the 6MWD as an important measure of clinical benefit in this pivotal Phase III study.

3.3.3 Rationale for Control Group

A placebo-treated control group will be used in this study to assess the differences in pulmonary function, 6MWD, PROs, and safety in patients who receive PRM-151 compared with patients who receive placebo. The use of a control group is necessary given the inherent variability in IPF progression in individual patients, IPF exacerbations, patients' lung function, and use of subjective assessments such as the PROs. Patients in the control group will undergo the same study assessments as the patients treated with PRM-151. All patients will be allowed to receive standard of care in addition to study drug throughout the study.

3.3.4 Rationale for Biomarker Assessments

IPF is a disease in which circulating levels of PTX-2 are lower in patients relative to healthy subjects (Murray et al. 2011) and may reflect retention of PTX-2 in the lung tissue due to localized biological activity. The disease is heterogeneous, with several pathways implicated in its pathobiology (Wolters et al. 2018). The rate at which IPF progresses is variable among individuals and potential biomarkers to predict this include CCL18 (Neighbors et al. 2018), MUC5B and telomere length (Dressen et al. 2018). Therefore, the study will include an exploratory component focused on identification of biomarkers that may be prognostic for patients likely to have an accelerated rate of disease progression. PD biomarkers including, but not limited to, CCL18 will be assessed to demonstrate evidence of biologic activity of PRM-151 in patients. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored. Biomarker samples collected during the study may be used to assess the relationship between IPF-related biomarkers, disease progression, clinical status, and treatment benefit.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 658 patients with IPF will be enrolled during the global enrollment phase of this study. After completion of the global enrollment phase, additional patients may be enrolled *in China, Hong Kong and Taiwan* in an extended China enrollment phase to ensure a total enrollment that is sufficient to support registration in China (see Section 3.1.1).

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 40–85 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the requirements of the study protocol, according to the investigator's best judgment
- Documented diagnosis of IPF per the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline (Raghu et al. 2018; Appendix 10)
- HRCT pattern consistent with the diagnosis of IPF, confirmed by central review of chest HRCT (available HRCT of acceptable quality performed within 12 months prior to screening or obtained during the screening period) and central review of lung biopsy (LB), if available. Details provided in Appendix 10.
- Minimum 6MWD of 150 meters with maximum use of 6 L/min at sea-level and up to 8 L/min at altitude (≥5000 feet [1524 meters] above sea level) of supplemental oxygen while maintaining oxygen saturation of ≥83% during the 6MWT during screening

- FVC ≥45% predicted during screening *as determined by the over-reader*
- Forced expiratory volume in 1 second (FEV_1)/FVC ratio >0.70 during screening *as determined by the over-reader*
- DLCO ≥30% and ≤90% of predicted during screening (Hgb corrected or uncorrected) *as determined by the over-reader*
- If receiving pirfenidone or nintedanib treatment for IPF, the patient must have been on treatment for at least 3 months and on a stable dose for at least 4 weeks prior to screening and during screening (with no contraindications according to local prescribing information)
- If not currently receiving nintedanib or pirfenidone treatment (either treatment naïve or having previously taken and discontinued) must have discontinued such treatment ≥4 weeks prior to screening and during screening

  If patient is considering starting treatment with either nintedanib or pirfenidone, patient must be on treatment for at least 3 months prior to screening, provided there are no contraindications according to local prescribing information.
- For women of childbearing potential *(excluding patients enrolling in Japan):* 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.
- Anticipated life expectancy of at least 12 months at baseline, according to the investigator's judgment
- Patient and investigator considered all medicinal treatment options and/or possibly lung transplantation prior to considering participation in the study. If the patient is on a lung transplant list, the investigator anticipates the patient will be able to complete the study prior to transplant.
- For patients enrolled in the extended China enrollment phase: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Evidence of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective-tissue disease, and drug toxicity)
- FVC% predicted value showing improvement in the 6-month period prior to screening and including screening value, as assessed by the investigator
- Emphysema present on $\geq$50% of the HRCT, or the extent of emphysema is greater than the extent of fibrosis, according to central review of the HRCT
- Receiving nintedanib in combination with pirfenidone
- Received cytotoxic, immunosuppressive, cytokine modulating, or receptor antagonist agents (including but not limited to methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine or other steroid sparing agent) within 4 weeks *prior to or during* screening
- Receiving systemic corticosteroids equivalent to prednisone $>$10 mg/day or equivalent within 2 weeks prior to *or during* screening
- 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 either during screening or prior to screening and not successfully resolved 4 weeks prior to screening visit
- *Positive* interferon gamma release assay *test for tuberculosis during screening*: Patients who have completed treatment for tuberculosis within 6 months prior to screening, and have no evidence of recurrent disease do not need to be tested.
- Resting oxygen saturation of $<89\%$ using up to 4 L/min of supplemental oxygen at sea level and up to 6 L/min at altitude (≥ 5000 feet [1524 meters] above sea level) during screening
- Co-existing acute or chronic medical condition that, in the investigator's opinion, would substantially limit the ability to comply with study requirements or may influence any of the safety or efficacy assessments included in the study
- Class IV New York Heart Association chronic heart failure
- Historical evidence of left ventricular ejection fraction $<35\%$
- Presence of pulmonary hypertension that, in the investigator's opinion, would substantially limit the ability to comply with study requirements or may influence any of the safety or efficacy assessments included in the study
- Cardiopulmonary rehabilitation program based on exercise training that has been completed within 8 weeks prior to screening or planned to start during the patient's enrollment in this trial
- History of smoking (including cigarette, cannabis, cigar, pipe and vaping) within 3 months prior to *or during* screening
- History of alcohol or substance use disorder within 2 years prior to *or during* screening or known or suspected active alcohol or substance-use disorder
- History of a malignancy within the 5 years prior to screening, with the exception of basal cell or squamous cell skin neoplasms. In addition, a malignant diagnosis or condition that occurred more than 5 years prior to screening, and any basal cell or squamous cell neoplasm must be considered cured, inactive, and not under treatment.
- Unable to refrain from use of the following:
  - Short acting bronchodilators (SABA) within 4 hours before pulmonary function, DLCO, and 6MWT assessments
  - Once daily, long-acting bronchodilators within 24 hours before pulmonary function, DLCO, and 6MWT assessments
  - Twice daily, long-acting bronchodilators within 12 hours before pulmonary function testing, DLCO, and 6MWT assessments
- Known post-bronchodilator response in FEV_1 and/or FVC $\geq 12\%$ and ≥ 200 mL, respectively

- Receipt of an investigational drug within 4 weeks, or 5 half-lives, whichever is longer, prior to *or during* screening
- Previous treatment with PRM-151
- History of severe allergic reaction or anaphylactic reaction to a biologic agent *including any allergies to the additives of the drug product.*
- Clinically significant abnormality on ECG during screening *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) *on ECG during screening,* based on the Fridericia correction formula
- *Clinically significant* laboratory *test abnormalities during screening* (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 during screening:
  - ALT and/or AST $\geq 2.5 \times$ upper limit of normal (ULN)
  - Total bilirubin $\geq 2 \times$ ULN
- Pregnant or breastfeeding, or become pregnant during the study or within 8 weeks after the final dose of PRM-151

  Women of childbearing potential must have a negative serum pregnancy test result within 30 days prior to initiation of study drug.
- *Women of childbearing potential (Only for patients enrolling in Japan)*
  - *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).*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: PRM-151 or placebo. Randomization will occur in a 1:1 ratio through use of a permuted block randomization method to ensure a balanced assignment to each treatment arm and will be stratified as follows:

- Concurrent use of nintedanib treatment versus pirfenidone treatment versus no concurrent treatment
- Geographic Region (China [including Hong Kong and Taiwan], North America [United States and Canada], Europe [including eastern Europe], Latin America, and Rest of World [including east Asia, Australia, and New Zealand])

4.2.2 Blinding

Patients and all study site personnel will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, the independent data coordinating center (iDCC) and independent Data Monitoring Committee (iDMC) members.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Plasma concentration (i.e., baseline, predose PK samples*, and some longitudinal sampling*) to measure the endogenous level of human pentraxin-2 [hPTX-2] will be analyzed from all patients *and will include* patients from the comparator arm. Baseline immunogenicity samples will be analyzed for all patients. Postbaseline immunogenicity samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

PRM-151 is a human recombinant form of a naturally occurring regulatory protein, and there is no known antidote to this protein in the event of a safety event. If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.8) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is PRM-151. Placebo is also considered an IMP in this study. The non-investigational medicinal products (NIMPs) for this study are pirfenidone and nintedanib. The NIMPs are considered background therapy for those patients already receiving either product when entering the trial and rescue therapy for any patient who commences treatment with either product during the trial.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 PRM-151 (*Zinpentraxin Alfa*)

PRM-151 Sterile Solution for Infusion is a 20 mg/mL solution of PRM-151 in 10 mM sodium phosphate, 5% (weight/volume [w/v]) sorbitol, and 0.01% (w/v) polysorbate 20 with a pH of 7.5. PRM-151 (*Zinpentraxin Alfa*) is supplied as a sterile concentrate in single use vials in clear borosilicate vials. The solution is clear to opalescent and essentially particle free. Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

CHO Gal-1 and CHO Gal-3 were identified in the first generation PRM-151 drug product. No new safety risks or no evidence on impact of efficacy were identified. An additional purification step will be applied to the second generation drug product and thus it will not contain detectable levels of CHO galectins. All patients enrolling onto the study after 1 June 2022, and randomized to the PRM-151 treatment arm will receive second generation PRM-151., whereas patients who enrolled into the study prior to 1 June 2022, and were randomized to the PRM-151 treatment arm, will continue receiving first generation PRM-151 for the remainder of the study.

4.3.1.2 Placebo

Placebo is a solution of 10 mM sodium phosphate, 5% (w/v) sorbitol, and 0.01% (w/v) polysorbate 20 with a pH of 7.5, matched to PRM-151 in total volume.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.2.

4.3.2.1 PRM-151 and Placebo

Patients will be randomized to receive the study drug PRM-151 or a PRM-151 matching placebo. Patients randomized to study drug will receive IV infusions of 10 mg/kg PRM-151 over 50 to 70 minutes, with dose based on the patient's weight taken at the same clinic visit (for loading or reloading doses, the weight taken at the first clinic visit for the first dose can be applied to the second and third doses). Patients randomized to placebo will receive IV infusions of placebo over 50–70 minutes. Refer to the pharmacy manual for more detail.

On all dosing days, dosing will occur after all efficacy and predose safety assessments scheduled for that visit are completed. Patients will receive treatment on study Days 1, 3, and 5, followed by infusions Q4W to Week 48. If any infusions are missed, repeat loading doses will be required at the next scheduled visit (three doses administered on alternate days).

Medical personnel authorized by the investigator will be responsible for the administration of study drug and for observation of each patient throughout the study. *At dosing visits, vital signs should be measured predose (within 60 minutes prior to dosing), every 15 minutes during the infusion, and 30−60 minutes postdose.* Patients should be observed for 1 hour post infusion to monitor for IRRs. Investigator, or designee, should assess whether any elements of the Sampson criteria were met after every infusion, as outlined in Appendix 5.

In the case of occurrence of signs and symptoms consistent with IRR, follow procedures and medication guidelines outlined in Section 5.

If the patient is not able to adhere to the dosing schedule of any doses, the study Medical Monitor should be contacted.

- To allow for flexibility around weekends, holidays, etc., the loading dose visits may occur over a time span of up to 8 days, with a minimum of 1 full calendar day between administration of doses (patients must not be dosed on consecutive days).
- Loading doses must be completed within an 8-day window. If any loading doses are missed or cannot be completed within the 8-day window, further doses must not be administered outside this period. In such instances, the patient will be required to repeat the loading dose regimen at the next scheduled visit.
- If the patient does not receive the scheduled dose within the specified visit window for the Week 4 visit or beyond, a protocol deviation will be documented, and the patient should be dosed as soon as possible within 3 weeks of the original scheduled visit.
- If the dose is delayed by >3 weeks beyond the original scheduled visit (within 1 week of the next scheduled dosing visit), the delayed dose is considered a missed dose and should not be administered. Dosing should resume with the next dose (reloading of three doses, as described above) according to schedule.
- After a missed or delayed dose, patients should keep following the dates on the original dosing schedule, and visit dates should not shift, unless otherwise directed by the investigator or study team (additional visits to allow for reloading of three doses will need to be scheduled).

In exceptional situations and following consultation with the Medical Monitor, if patients cannot attend the study site for a scheduled infusion, administration of study drug may be permitted in other settings (e.g., at a different investigational site). Patient safety must be prioritized when utilizing off-site procedures (e.g., ensuring staff are appropriately qualified to deliver the infusion and are trained to monitor for and manage anaphylaxis and IRRs). In such circumstances, infusion-related safety data, safety laboratory assessments, and PK/PD samples may also be collected off-site.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study (PRM-151 and placebo) will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS, to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature

conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the PRM-151 Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to PRM-151

Patients may be eligible to receive PRM-151 as part of an OLE study planned by the Sponsor. Eligible patients will be able to receive PRM-151 until the drug is commercially available in their country for IPF or the Sponsor decides to terminate the trial. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 30 days prior to initiation of study drug to the study completion or discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. *Additionally, all COVID-19 vaccinations received at any time in the past (even prior to 30 days before screening) should be recorded on the Concomitant Medications eCRF.*

All past anti-fibrotic therapy will be recorded in the Prior and Concurrent Anti-fibrotic Use form of the eCRF.

4.4.1 Permitted Therapy

There are no restrictions on the use of any concomitant medication required for the treatment of an emerging medical condition (adverse event) while a patient is enrolled in the trial. In such cases, all available therapies should be provided for the optimal medical management of the patient, including use of systemic corticosteroids in the event of acute exacerbation of IPF if deemed indicated by the treating physician. For guidance on the use of pirfenidone or nintedanib, see Section 4.4.3. Additionally, use of the following medications as part of routine care is allowed:

- Chronic maintenance, low-dose oral corticosteroid use *(equivalent to prednisone* $\leq$10 mg daily) is permitted. Short-term, higher doses of corticosteroid may be required for acute medical emergencies (e.g., adrenal insufficiency or acute exacerbations of IPF) and is permitted, along with subsequent corticosteroid dose tapering. Reasons for corticosteroid use should be clearly documented in the eCRF.
- Inhaled bronchodilator agents, except for restricted use in the 12- to 24-hour period preceding efficacy assessment measures (see Section 4.5.6)
- Initiation of or change in supplemental oxygen therapy as clinically indicated, except when performing the 6MWT, when oxygen usage should be maintained at the baseline oxygen flow rate established by the oxygen titration procedure conducted during screening (see Section 4.5.7)
- *Approved vaccinations, including COVID-19 vaccinations*

4.4.2 Prohibited Therapy

To avoid potential interactions of therapeutic agents that may interfere with either the safety or efficacy assessments, use of the following medications are prohibited during the study:

- All investigational therapies, within 4 weeks (or 5 half-lives, whichever is longer) before screening and during study participation
- Any newly approved anti-fibrotic therapy that becomes available during the study
- Short-acting bronchodilator use within 4 hours before pulmonary function, DL_{CO}, and 6MWT assessments
- Once daily, long-acting bronchodilators within 24 hours before pulmonary function testing, DLCO, and 6MWT assessments
- Twice daily, long-acting bronchodilators within 12 hours before pulmonary function testing, DLCO, and 6MWT assessment
- Immune-suppressants (e.g., methotrexate, azathioprine, cyclophosphamide, cyclosporine, everolimus, or other immune-suppressants, including those used after organ transplant) within 4 weeks before baseline (Dosing Day 1) and during the study

- *High-dose corticosteroids (equivalent to prednisone >10 mg daily) unless clinically indicated as per Section 4.4.1.*
- Strong inhibitors or inducers of CYP1A2 in patients taking pirfenidone
- Potent inhibitors or inducers of P-gp in patients taking nintedanib
- Combined treatment with pirfenidone and nintedanib

In addition, cardiopulmonary rehabilitation programs should not be initiated during the study.

4.4.3 Use of Pirfenidone or Nintedanib

Standard-of-care anti-fibrotic therapy (pirfenidone or nintedanib) is permitted during the study, if not contraindicated according to local prescribing information. Patients must have been on treatment for at least 3 months and a stable dose for at least 4 weeks prior to and during screening, and during the study.

For all patients receiving anti-fibrotic therapy, the investigator should document the dose and regimen of the anti-fibrotic drug. For patients not receiving anti-fibrotic therapy during the study, the investigator should document the reason(s). All historic and current use, including changes in pirfenidone or nintedanib doses and reasons for change must be recorded in the eCRF.

- Patients are expected to remain on their specific dose and regimen of nintedanib or pirfenidone throughout the study duration, although a patient may stop, dose reduce, re-start, or dose increase nintedanib or pirfenidone treatment during the study for safety or tolerability reasons, in accordance with local prescribing information. All reasons for dose changes must be documented in the eCRF.
- In addition, patients may switch from nintedanib to pirfenidone (or vice versa) during the study if clinically indicated and if not contraindicated according to local prescribing information. The investigator may consider discussing changes in anti-fibrotic therapy with the Medical Monitor throughout the study.
- If not on nintedanib or pirfenidone treatment for IPF at study entry, patients must have been off treatment for a minimum of 4 weeks before Screening or been treatment naive (i.e., never taken the medications). During the study, patients may initiate (naive users) or re-start (prior users) nintedanib or pirfenidone, as rescue, if determined to be clinically indicated by the investigator upon follow-up examination performed after the Baseline Dosing visit (Day 1), providing there are no contraindications according to local prescribing information. The investigator may consider discussing changes in anti-fibrotic therapy with the Medical Monitor throughout the study. Patients who start rescue therapy will be encouraged to remain in the study and continue study treatment.
- Combination use of pirfenidone and nintedanib is not allowed in the study.

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1, Appendix 2, Appendix 3*, and Appendix 4*. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and laboratory test values from the previous visit are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. At screening, each patient will be assessed for eligibility against the study entrance criteria (Section 4.1). Screening assessments may be performed during one visit or over multiple days during this 4-week period, and consideration should be given to the sequence of conducting the screening evaluations, with less invasive testing performed first (e.g., medical history review, central laboratory tests), followed by more involved testing (e.g., 6MWD, chest HRCT). *From baseline or dosing day 1 onwards, the sequence* of assessments should be followed *as per* Table 2. Prior to any invasive testing, the site should verify that the historic HRCT scans (if not planned to be conducted during screening) and LB (if applicable) have been conducted and will be able to be retrieved at the start of the screening period in order to be sent for central review. Site should make sure that test conditions for each test are optimal at time of testing. Patients who do not meet the study entrance criteria will not be allowed to participate in the study. However, for select reasons, patients who do not meet the criteria for participation may be eligible for rescreening once. The reason(s) for the patient's ineligibility for the study will be documented in a site screening log. Once a patient has met all eligibility criteria, they can be randomized immediately (i.e., they do not need to wait for the 4-week screening period). No baseline assessments or procedures should be performed until randomization has taken place.

4.5.2 Sequence of Assessments

On dosing days, dosing will occur after all safety and efficacy assessments scheduled for that visit are complete. Assessments should be completed as shown in Table 2. For loading or reloading doses, scheduled efficacy assessments will only be performed on the first of the three loading dose days.

Table 2 Sequence of Assessments

Sequence	Assessments
1	• Patient-reported outcomes (*PRO*) (in following order): – SGRQ – UCSD-SOBQ – EQ-5D-5L
2	• Medical history, review of concomitant medications, vital signs, physical examination, and ECG
3	• Pulmonary function tests (in following order): – Spirometry – DLCO 30-*60* minute break – 6MWT
4	• HRCT (when completed on same day as other assessments) [a]
5	• Laboratory samples
6	• Study drug administration [b]
7	• *Post-infusion laboratory samples* (see Appendix 2–Appendix 4)

6MWT = 6-minute walk test; DLCO = diffusing capacity for carbon monoxide; eCRF = electronic Case Report Form; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; HRCT = high-resolution computed tomography; OLE = open-label extension; SGRQ = St. George Respiratory Questionnaire; UCSD-SOBQ = University of California, San Diego–Shortness of Breath Questionnaire.

[a] *Performed at week 52 for patients who had a HRCT scan as part of screening. In* order to allow flexibility in scheduling, the HRCT can be performed at an earlier time on a different day. For patients participating in the OLE study, the Week 52 HRCT should be performed before any dosing in the OLE study. Efficacy measurements should be collected as outlined in the schedule of activities.

[b] In exceptional circumstances, if the site is unable to perform all study assessments on the same day or at the same site, study drug infusion may be administered up to 48 hours after the on-site efficacy assessments, provided that these are completed within the 5-day visit window. However, the sequence of assessments must be maintained, and all efforts should be made to complete study assessments on the same date.

4.5.3 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including number of years since IPF diagnosis, *family history of IPF,* clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and alcohol and substance use,

that occurred prior to time of first dose of study drug should be reported as medical history *on the General History and Baseline Conditions eCRF*, including:

- Pulmonary hypertension
- Chronic obstructive pulmonary disease (COPD)/Emphysema
- Lung cancer
- Obstructive sleep apnea
- Pulmonary embolism
- Respiratory infections *(including tuberculosis)*
- Cardiovascular disease and risk factors, including arrhythmias, cardiac failure or congestive heart failure, ischemic heart disease, cerebrovascular disease and stroke, peripheral artery disease systemic arterial hypertension, hypercholesterolemia/hyperlipidemia,
- Participation in supervised pulmonary or cardiac rehabilitation programs
- Past surgical history

All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days prior to initiation of study treatment will be recorded *on the Concomitant Medications eCRF.* At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. History of anti-fibrotic therapy should also be documented since IPF was diagnosed (i.e., pirfenidone and nintedanib treatment, dose, duration of therapy, reasons for discontinuation, if applicable). *Additionally, history of all COVID-19 vaccinations received in the past should be documented.*

Patient demographic information including age, sex, and self-reported race/ethnicity will be recorded in the screening period for all patients, where allowed per local regulations.

4.5.4 Physical Examinations

A complete physical examination, performed during screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Height will be recorded during screening for all patients. Weight will be recorded at each dosing visit (except for the second and third loading doses).

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, oxygen saturations, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

At dosing visits, vital signs *should* be measured predose (within 60 minutes prior to dosing), every 15 minutes during the infusion, and 30–60 minutes postdose.

4.5.6 Pulmonary Function Tests

Standardized spirometry equipment and procedure guidelines will be provided to all study sites. As some PFTs are considered aerosol-generating procedures, additional precautions to reduce potential spread of infection should be taken in accordance with local guidance. Spirometry will be performed according to ATS/ERS guidelines (as referenced in the PFT manual) as per the schedule of activities (see Appendix 1). Details on PFT procedures are available in the PFT manual. PFT data will be sent for central review.

DLCO will be measured according to ATS/ERS guidelines (as referenced in the PFT manual). *DL_{CO} will be performed using local equipment as this will not be provided by the Sponsor to study sites.*

Acceptability of the spirometry and DLCO data from the computerized system (including screening assessments) will be determined by over-readers blinded to study drug treatment (comprising graphic representations of the maneuvers as well as numerical results). Calculations for the reproducibility of the acceptable maneuvers will be performed and reviewed centrally by over-readers blinded to study drug treatment. *Only data from acceptable over-read spirometry and DL_{CO} maneuvers will be used for eligibility confirmation and data analysis.*

The screening spirometry and/or DLCO sessions may be repeated once, if the initial session is rejected by the over-reader. This is the only session during the study that may be repeated. In extenuating circumstances, one further spirometry and/or DLCO session may be attempted after discussion with the Medical Monitor. No more than three spirometry and/or DLCO sessions should be performed during the screening period. Repeat sessions are only permitted following rejection of previous sessions by the over-reader.

On visits at which spirometry and DLCO are to be performed spirometry should be performed first, followed by DLCO, and then 6MWT.

Inhaled bronchodilator use in the 12- to 24-hour period prior to PFTs and the 6MWT is restricted:

- Short-acting bronchodilator should not be used within 4 hours before pulmonary function, DLCO, and 6MWT assessments.
- Once daily*,* long-acting bronchodilators should not be used within 24 hours before pulmonary function testing, DLCO, and 6MWT assessments.
- Twice daily*,* long-acting bronchodilators should not be used within 12 hours before pulmonary function testing, DLCO, and 6MWT assessments.

4.5.7 Six-Minute Walk Test

Conduct of the 6MWT will be carefully defined and controlled according to the criteria defined and validated by du Bois et al. (2011), with additional control measures suggested in the ERS/ATS Guideline for field walking tests (Holland et al. 2014):

- The test will be performed indoors on a flat, straight corridor with a hard surface at least 30 m in length.
- An oxygen titration procedure will be performed at the Screening for patients who require supplemental oxygen during the 6MWT (up to 6 L/min of oxygen at sea level, and up to 8 L/min at altitude [>5000 ft]) *to establish a baseline flow rate. The oxygen titration procedure should be conducted as per local standard practice.*
- Before each 6MWT, patients will be required to have resting oxygen saturation as measured by pulse oximetry of at least 89% after 10 minutes of rest breathing room air, or at the baseline oxygen flow rate as established during the titration procedure.
- Patients will be instructed to walk as far as they can without jogging or running; if they need to slow down or stop to rest, they will be permitted to do so and encouraged to resume walking as soon as they are able.
- The test will be stopped if the patient experiences chest pain, intolerable dyspnea, leg cramps, diaphoresis, or desaturation below 83% for at least 10 seconds.
- The pre-test conditions for oxygen use will be maintained throughout the study as much as possible, as noted at the Day 1 visit prior to first dose.

As previously described, the 6MWT assessment should be performed after completion of PRO questionnaires and after PFTs, allowing for a short recovery period from the PFTs. In the rare instance that it is not possible to complete the 6MWT last, allow a 30-*60* minute recovery time before continuing with the next efficacy assessment.

A procedure manual and training video (video instructions) detailing the testing method recommended by the ATS and the European Respiratory Society (ATS 2002; Holland et al. 2014) for the 6MWT will be provided separately. These materials will include detailed instructions for standardized execution of the 6MWT, and describe the equipment and personnel required to conduct the assessment as well as the testing methods.

The Borg Scale of Perceived Exertion (Appendix 11) will be assessed just prior to and immediately following the completion of the 6MWT.

4.5.8 High-Resolution Computed Tomography

Pulmonary HRCT scans will be reviewed during screening to confirm the IPF diagnosis. Good-quality standard of care scans obtained ≤12 months prior to screening and in accordance with study image acquisition guidelines can be used for eligibility determination. *If a HRCT scan meeting the image acquisition guidelines is not available, a new HRCT scan should be obtained during screening.* HRCT scans will be reviewed first by the site radiologist and/or investigator to assess for eligibility. If the site determines that the patient's HRCT meets IPF diagnostic criteria as specified in Appendix 10, the HRCT scans will be sent for central review to confirm eligibility. The blinded central review radiologists will evaluate screening images in accordance with the 2018 *IPF* Clinical Practice Guidelines by ATS, the ERS, JRS, and the ALAT (Raghu et al. 2018), *and determine the extent of emphysema on the scan, if present.* Final eligibility will be determined by the central review assessments, inclusive of lung biopsy, if available.

Randomized patients who undergo protocol-specified HRCT scan during screening will undergo repeat imaging at the Week 52 visit.

4.5.9 Lung Biopsy

Lung biopsies are not required for eligibility into the study *and are not required during the study*. Patients who have undergone a lung biopsy (including cryobiopsy) to support the diagnosis of IPF, should have the relevant slides sent for central review assessment to confirm eligibility in accordance with the ATS/ERS/JRS/ALAT *IPF* Clinical Practice Guideline (Raghu et al. 2018). The central review pathologists will evaluate submitted slides for UIP pattern. The histopathologic assessment criteria are outlined in Appendix 10.

4.5.10 Assessment of Acute Exacerbations of IPF, Hospitalizations for Respiratory Causes, and Deaths (Adjudicated Events)

An independent, blinded *Clinical* Adjudication Committee will be convened to review all available data for all potential cases of acute exacerbations of IPF, hospitalizations for respiratory causes, and all deaths. This *Clinical* Adjudication Committee will be comprised of pulmonary disease physicians familiar with IPF exacerbations. A charter for the *Clinical* Adjudication Committee will provide further details. The *Clinical* Adjudication Committee will determine if the reported events meet the criteria of acute exacerbation of IPF, hospitalization for respiratory causes, and deaths (including deaths related specifically to respiratory causes) as defined in the charter.

4.5.10.1 Acute Exacerbations of IPF and Suspected Acute Exacerbations of IPF

Acute exacerbation of IPF is defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality, marked by the following diagnostic criteria (Collard et al. 2016):

- Previous or concurrent diagnosis of IPF
- Acute worsening or development of dyspnea typically <30 days in duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
- Deterioration not fully explained by cardiac failure or fluid overload

Acute exacerbations of IPF are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found (e.g., infection, post-procedural/postoperative, drug toxicity, aspiration).

Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet all four diagnostic criteria owing to missing computed tomography data are termed "suspected acute exacerbations of IPF."

At each study visit, the investigator will ask directed questions and review the patient file to assess the possibility that the patient experienced an acute IPF exacerbation since the preceding study visit. An acute IPF exacerbation should be reported as an adverse event of special interest (see Section 5.3.3) (or serious adverse event as applicable).

All relevant adverse event data (summary on clinical course, signs and symptoms; laboratory, lung function and imaging results; and treatment provided, including hospitalizations) relating to the exacerbation must be collected and entered onto the adverse event form. A charter for the *Clinical A*djudication Committee describes the process for the data to be reviewed and criteria for defining an IPF exacerbation.

4.5.10.2 Hospitalizations for Respiratory Causes

Hospitalizations for respiratory causes are defined as non-elective hospitalizations due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF. All investigator-reported hospitalizations for respiratory causes will be assessed by an independent *Clinical* Adjudication Committee, as described in the charter.

4.5.10.3 Deaths Due to Respiratory Causes

All deaths occurring during the study must be recorded. The event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept on the Adverse Event eCRF.

All investigator-reported deaths will be assessed by an independent *Clinical* Adjudication Committee to determine whether each death was related to IPF, another respiratory cause, or an alternative (non-respiratory and non-IPF) cause.

4.5.11 Health Care Utilization for Respiratory Events

The following events will be recorded as health care utilization for respiratory events:

- Unscheduled visits to a healthcare professional/clinic for any respiratory event
- Urgent care or emergency room visits for respiratory events
- Hospitalization days for a respiratory cause, including for exacerbation of respiratory symptoms
- During hospitalization, any stay in ICU, including ICU days

4.5.12 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (lymphocytes, eosinophils, neutrophils, monocytes, basophils)
- Serum chemistries and liver function tests (LFTs): chloride, potassium, BUN, creatinine, albumin, AST, total bilirubin, sodium, bicarbonate (CO_2), calcium, glucose, ALK, ALT, total protein, C-reactive protein (CRP), eGFR
- Coagulation tests: PT, PTT, INR
- Pregnancy test *(Excluding patients enrolled in Japan)*
- All women of childbearing potential will have a serum pregnancy test during screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- SARS-CoV-2 serology testing (IgM, IgG)
- Tuberculosis test: interferon gamma release assay

    Patients who have completed treatment for active or latent tuberculosis within 6 months prior to screening, and have no evidence of recurrent disease, do not need to be tested

In exceptional situations, upon Sponsor approval, laboratory samples may be collected off-site.

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Serum sample for ADA analysis

- Serum sample for tryptase *and complement C3* in case of ≥*Grade 2* IRRs or suspected anaphylaxis *or hypersensitivity reactions*
- PRM-151 plasma sample for PK *analyses*

  Blood samples for determination of PRM-151 concentration are to be collected from all IPF patients for PK measurements (see Appendix 2), patients enrolled in China and Hong Kong and Taiwan (see Appendix 3), *and all patients enrolled in Japan (see Appendix 4).*
- Serum and plasma samples for biomarker analysis
- Blood PAXgene for RNA biomarker analysis

  PAXgene for RNA biomarker analysis is not applicable for Chinese patients enrolled in mainland China.

Circulating blood biomarkers that may provide information on the course of fibrosis will be collected. The IPF-related biomarkers that will be investigated may include, but are not limited to, CCL18, osteopontin, CXCL13, periostin, and COMP. Longitudinal samples will be used to assess IPF-related biomarker changes over time. Screening and baseline samples will be used to assess the relationship of IPF-related biomarkers with clinical status, disease progression, and treatment benefit. If novel PTX-2 or IPF-related biomarkers are identified, they may be measured from stored blood, serum, or plasma.

Exploratory biomarker research may include, but will not be limited to MUC5B and telomere length measurement. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Genomic research will be aimed at exploring inherited characteristics. NGS methods may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, but only at participating sites (see Section 4.5.15).

Screening blood samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.16), biological samples will be destroyed

no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; PK and ADA samples collected for study-related analyses will be stored for up to 5 years after the final study results have been reported.
- Blood *and other* samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed, unless the patient consents optionally to have leftover samples retained as part of the Research Biosample Repository (RBR; see Section 4.5.16). However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, *the results are extremely unlikely to impact any clinical decision making, and* data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.13 Electrocardiograms

ECG will be collected prior to study drug dosing at selected visits (see Appendix 1). Apart from the scheduled assessment, ECG may also be collected in the event of an IRR as soon as possible after stabilization of the patient.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. ECGs for each patient should be obtained from the same machine whenever possible to minimize variability. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. Scheduled ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG

resting period and during ECG recording. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings.

Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. De-identified copies of all ECGs will be electronically transmitted or mailed for storage centrally at a designated contract research organization (CRO).

Clinically significant ECG abnormalities should be reported as adverse events. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

4.5.14 Clinical Outcome Assessments

PRO instruments will be completed to assess the treatment benefit and patient experience of PRM-151. PRO data will be collected through use of the following instruments: SGRQ, UCSD-SOBQ, and EQ-5D-5L (assessed in that order).

4.5.14.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

During clinic visits, instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.

- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.14.2 Description of Clinical Outcome Assessment Instruments

St. George's Respiratory Questionnaire

The SGRQ is a 50-item respiratory-specific quality-of-life questionnaire initially developed and validated for use in COPD (Jones et al. 1992; see Appendix 6). It includes questions that assess the impact of disease on symptoms, activity, and functionality. The symptom scale assesses the severity of respiratory symptoms, the activity scale examines impairment in patient activity as a result of respiratory symptoms, and the impact scale evaluates effects of respiratory symptoms on overall function and well-being. Each scale is scored from 0 to 100, and a total score represents the weighted average of these three subscores. Items are assessed on various response scales, including a 5-point Likert scale and a true/false scale. The SGRQ has a recall period of the past 4 weeks.

University of California, San Diego–Shortness of Breath Questionnaire

The UCSD-SOBQ is a 24-item questionnaire used to assess dyspnea severity during specific activities (21 items) and limitations caused by dyspnea in daily life (4 items) (See Appendix 7). Items are assessed using a 6-point Likert scale and summed to produce a total score ranging from 0–120, with higher scores reflecting greater dyspnea severity. Respondents are asked to provide their answers based on an average day during the past week.

EuroQol 5-Dimension Questionnaire, 5-Level Version

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 8). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status.

4.5.15 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable telomere length measurements and WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge

and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.15) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

No sites in mainland China will participate in this sample/data collection.

Refer to Section 4.5.12 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.16 Optional Samples for Research Biosample Repository

4.5.16.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.16.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.16) will not be applicable at that site.

4.5.16.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to PTX-2 or PRM-151, diseases, or drug safety:

- Peripheral blood mononuclear cell (PBMC) samples collected during screening and 1–2 hours postdose on *Days* 1 and *5, and on* Weeks 4 and 12
- *Urine samples collected per Appendix 2 and Appendix 4.*
- Leftover blood, serum, plasma, urine, and PBMC samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)
- *An optional DNA sample will be collected once at any visit if site declines participating in the collection of blood samples for WGS and WES.*

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods, including telomere length measurements. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

RBR samples will not be collected from Chinese patients that are enrolled in the study (both in the global and extended China enrollment phases) in mainland China.

4.5.16.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.16.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be

required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.16.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.16.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

*It should be noted that study treatment discontinuation and p*atient *discontinuation from the study are managed differently, as follows:*

- *Patients who discontinue study treatment will continue with study visits and assessments (without continuing to receive study drug treatment)*
- *Patients who discontinue from the study will be invited to enroll in the OLE study for long-term follow-up of survival data, if they do not wish to continue with study drug treatment and* other assessments and visits.

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Anaphylaxis or serious hypersensitivity reaction
- Grade 4 IRR or two Grade 3 IRRs
- Lung transplant

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

If a patient discontinues study drug treatment prematurely for any reason, the patient will be encouraged to complete all planned study visits *and assessments (except for IMP administration)* through *to* Week 52. If unable to return for the remaining protocol visits *through to week 52*, patients will return to the clinic for a treatment discontinuation visit 4 weeks after the final dose of study drug (see Appendix 1 for additional details). Every effort should be made to collect spirometry, 6MWD, safety, and survival data at *the* time of the Week 52 or treatment discontinuation visit.

4.6.2 Patient Discontinuation from the Study

Patients will return to the clinic for a study completion or study discontinuation (end of study *[see week 56 of* Appendix 1]) visit 4 weeks after the treatment completion or treatment discontinuation visit (8 weeks after the final dose of study treatment).

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

Patients will be invited to enroll in the OLE study for long-term follow-up of survival data if the patient does not wish to continue with study treatments or other assessments and visits.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

PRM-151 is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with PRM-151 in completed and

ongoing studies. The anticipated important safety risks for PRM-151 are outlined below. Please refer to the PRM-151 Investigator's Brochure for detailed safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria treatment interruption or discontinuation, are provided below.

If patients have been prescribed pirfenidone or nintedanib, this should comply with local prescribing information. Patients should adhere to the instructions and recommendations stated in the respective local labels. Investigators should consult local prescribing information for management of adverse events, including guidance on dose reductions and discontinuation of these treatments.

In exceptional circumstances, if patients cannot attend a study site for a scheduled visit, patients should be followed up ideally by telephone around the time of the scheduled visit to collect information on any adverse events and changes to concomitant medications.

Pandemic Preparedness

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for infections prior to and during study participation should be considered according to local or institutional guidelines or those of applicable professional societies.

5.1 POTENTIAL RISKS ASSOCIATED WITH PRM-151

Potential risks for PRM-151 include infusion-related reactions (IRRs), anaphylactic and hypersensitivity reactions, post-implantation fetal loss, and immunogenicity. Outlined below is the safety plan for managing the potential risks of IRRs, anaphylactic and hypersensitivity reactions, and post-implantation fetal loss. Refer to the latest IB for further information.

Infusion-related reaction (see Section 5.4.5.1) is a temporal and causality-based event. This is not a clinical syndrome or medical concept and cannot be characterized by clinical criterion. Whereas, hypersensitivity reaction is considered as an immune related reaction which can be immediate or delayed. There is a great degree of overlap in signs and symptoms between IRR and hypersensitivity reaction. Investigators should use their medical judgement to assess if an event is immune mediated.

5.1.1 Infusion-Related Reactions

IRR risks associated with PRM-151 are inherent in it being the recombinant form of a naturally occurring human protein. PRM-151 has an endogenous counterpart, and ADAs could potentially affect the efficacy of PRM-151 treatment in addition to having the potential to cross-react with endogenous hPTX-2. Patients should be monitored for IRRs*, which may occur within 24 hours of administration of PRM-151*.

Signs and symptoms of an infusion reaction may include the following: headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, hypotension, lightheadedness, palpitations, urticaria, and somnolence. Although unlikely, serious allergic reactions (e.g., anaphylaxis) may occur at any time during the infusion.

In the Phase II study (PRM-151-202; n = 116), 2 patients (2.6%) treated with PRM-151 experienced IRRs during the randomized period (in Weeks 1 and 8), and 10 patients (9.0%) treated with PRM-151 during the OLE period (occurring from Weeks 28 to 108). All IRRs were either Grade 1 or 2 except for one Grade 3 IRR.

5.1.2 Anaphylactic and Hypersensitivity Reactions

Anaphylactic and hypersensitivity reactions are considered a potential risk with all biologic medications, including PRM-151. Appropriate precautions should be taken to ensure appropriate measures to manage anaphylaxis are available. *PRM-151 was found to contain small amounts of the sugar α-Gal (Section 1.2.2). The α-Gal epitope is present in red meat, the gastrointestinal tract of ticks with long shells, and also in some drugs of animal origin (e.g., porcine or bovine gelatin) and therapeutic chimeric monoclonal antibodies (e.g., cetuximab). In patients presenting immunoglobulin E (IgE) sensitization to α-Gal (e.g., red meat allergy or a history of tick bites), clinical allergic reactions having immediate onset may be induced by the first parenteral exposure to drugs containing α-Gal (Popescu et al. 2019). As a result, the risk of anaphylactic or hypersensitivity reactions may be increased in patients with a history of tick bites, red meat allergy, or patients with IgE antibodies directed against α-Gal. More information on the presence of α-Gal in PRM-151 is provided in the PRM-151 IB.*

In Phase I/II clinical trials of PRM-151 to date, one event was reported as an anaphylactic reaction in a patient taking part in the Phase II study (PRM-151G-101) in patients with myelofibrosis. The event occurred 17 days following the fifth dose of PRM-151 (for additional details see the PRM-151 Investigator's Brochure).

Investigators and health care professionals administering study treatment should be trained to recognize and manage the signs and symptoms of a potential anaphylactic, or hypersensitivity reaction and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; *Appendix 5*). Investigators and health care

professionals should also be trained to accurately and appropriately report these events immediately to the Sponsor as adverse events of special interest and as serious adverse events, if appropriate (see Section 5.5). Health care professionals should also instruct patients on how to recognize the symptoms of any anaphylactic, or hypersensitivity reactions, and to contact a health care provider or seek emergency care in case of any such symptoms. Patients will need to be clinically stable prior to each dose of study drug as assessed by clinical evaluations, including vital signs and spirometry measurements.

If a patient experiences a suspected and/or non-serious hypersensitivity reaction, the case should be discussed with the Medical Monitor prior to continued dosing. If a patient has signs or symptoms of an anaphylactic or serious hypersensitivity reaction, administration of the study drug must be discontinued permanently.

The patient should be treated according to the standard of care for management of anaphylaxis or hypersensitivity reaction.

5.1.3 *Post-implantation Fetal Loss*

In a rabbit dose range finding embryo fetal development study, PRM-151--related adverse effects at 60 mg/kg/day included a high number of embryo-fetal deaths, post-implantation loss rate, high placental remnant rate, and lower fetal viability rate. At 200 mg/kg/day, PRM-151 treatment resulted in complete post-implantation fetal loss.

No pregnancies have been reported across any of the completed Phase 1 and 2 studies with PRM-151.

In this study, women of childbearing potential (WOCBP) 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. Additionally, women of childbearing potential enrolling from sites in Japan are excluded from the study. Male subjects with a female partner of childbearing potential or pregnant female partner must remain abstinent or use a condom during the treatment period and for 8 weeks after the final dose of PRM-151.

5.1.4 Management Guidelines for Infusion-Related Reactions, Anaphylactic and Hypersensitivity Reactions

If an IRR *Grade* ≥ 2 event occurs, the steps outlined in Table 3 should be followed. *For Grade 1 IRRs, investigators should treat as per medical judgement or local procedures.*

Table 3 Actions if an *Infusion-Related Reaction (Grade ≥2)* Occurs

Event	Actions
IRR Event Occurs	If NCI CTCAE Grade 2 (Section 5.4.3) signs and symptoms are present: • Treat per local guidelines. • Reduce rate of study drug infusion (to 120 minutes). • Collect ECG and after patient stabilizes, collect labs (serum tryptase [a], ADA*, PK sample*, complement C3). • Capture signs and symptoms per Sampson criteria. If NCI CTCAE Grade 3 signs and symptoms are present: • Treat per local guidelines. • Stop study drug infusion. • Collect ECG and after patient stabilizes, collect labs (serum tryptase a, ADA, *PK sample,* complement C3). • Capture signs and symptoms per Sampson criteria. If NCI CTCAE Grade 4 signs and symptoms are present or a patient experiences a second occurrence of a Grade 3 IRR, in addition to the above guidance for a Grade 3 IRR event: • Permanently discontinue study drug treatment.
IRR (Grade 2 and Grade 3 [1st occurrence]) resolved after treatment and/or reduced infusion rate	• Complete study drug infusion at reduced rate (120 minutes). • Closely monitor patient.
IRR not resolved after treatment and/or reduced infusion rate	• Stop study drug infusion. • Treat and closely monitor patient.
IRR *(Grade 2 and Grade 3 [1st occurrence])* resolved after continued treatment	• Restart study drug infusion at reduced rate (120 minutes). • Next study drug infusion should be at reduced rate and premedication should be used. b • Subsequent study drug infusions may be at reduced rate with premedication. • *Please note, if a patient experiences a second occurrence of a Grade 3 IRR or a Grade 4 IRR event, study drug treatment must be permanently discontinued.*

ADA = anti-drug antibody; IRR = infusion-related reaction*; PK = pharmacokinetics*; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] *Serum tryptase should be collected between 1 - 6 hours after the event*

[b] Diphenhydramine or clemastine and dexamethasone are recommended (see details in text below).

The next study drug infusion after *a Grade ≥ 2* IRR *or non-serious hypersensitivity reactions* should be infused over 120 minutes and the following premedications are recommended for all subsequent study drug administrations after *these events*:

- Diphenhydramine 50 mg IV or clemastine 2 mg IV (or an equivalent dose of an antihistaminic drug)*; recommended timing of premedication: 30 minutes prior to infusion*
- Dexamethasone 10 mg IV (or an equivalent dose of a long-acting corticosteroid)*); recommended timing of premedication: 60 minutes prior to infusion*

If subsequent infusion(s) are uneventful, the investigator may resume 50- to 70-minute infusions of study treatment and may discontinue premedication.

Suspected IRRs (Grade ≥2*), anaphylactic, and hypersensitivity (all grades) reactions* must be reported as an Adverse Event of Special Interest as described in Section 5.3.3. See reporting of IRRs discussed in Section 5.4.5.1.

Assessment of potential anaphylaxis will be conducted at every infusion per the clinical criterion for diagnosing anaphylaxis as described by Sampson et al. 2006 NIAID/FAAN (*Appendix 5*). Patients experiencing suspected anaphylaxis *or hypersensitivity reaction* should be managed as per local guidelines. *If a patient experiences suspected anaphylaxis and/or hypersensitivity reaction regardless of seriousness or severity, an ECG should be collected after the patient stabilizes. Blood* samples *for ADA,* serum tryptase, complement C3*, and PK analysis should be obtained at the time of the event whenever possible (serum tryptase should be collected between 1 and 6 hours after the event), and a blood sample for ADA, serum tryptase, and complement C3 should be obtained at the first follow-up visit after the event.*

All potential anaphylaxis cases reported by investigators to the Sponsor will be subsequently submitted for adjudication to a blinded Anaphylaxis Adjudication Committee, composed of external experts in allergic diseases. The committee will assess whether the reported event is a true anaphylaxis event (based on Sampson's criteria) and whether the reported anaphylaxis event is causally related to study treatment.

If a patient has signs or symptoms of an anaphylactic or serious hypersensitivity reaction (including events deemed to have met the criteria as described by Sampson according to the blinded Anaphylaxis Adjudication Committee), administration of the study drug must be discontinued permanently.

The anaphylaxis adjudication process has been outlined in the Anaphylaxis Adjudication *Committee* Charter.

5.2 MANAGEMENT OF PATIENTS WHO EXPERIENCE ADVERSE EVENTS

5.2.1 Dose Modifications

Dose modifications of PRM-151 or matching placebo are not permitted in the study.

5.2.2 Treatment Interruption

Study treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. Resumption of study treatment should be discussed with the Medical Monitor.

In the event that one or more doses of PRM-151 or placebo is missed, the patient will be required to reload with three doses of study treatment at the next scheduled visit, allowing alternate days between infusions. Reasons for any such dose interruptions should be recorded in the eCRF. The investigator should discuss with the Medical Monitor prior to reloading after a dose is missed due to an adverse event.

5.3 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.5.

5.3.1 Adverse Events

According to the International Council for Harmonisation (ICH) guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.4.5.9 and 5.4.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.3.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
- This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.4.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.4.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2 for reporting instructions).

5.3.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.5.2 for reporting instructions). Adverse events of special interest for this study are as follows.

Adverse events of special interest related to drug development in general:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.4.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Adverse events of special interest relevant to PRM-151:

- Suspected Infusion Related Reaction with NCI CTCAE Grade ≥ 2
- Suspected anaphylactic or hypersensitivity reactions (all grades)
- Acute or suspected exacerbation of IPF (all grades)

5.3.4 Collection of Survival Data

All efforts should be made to collect the survival data even if the patient cannot physically be present for the visit.

Survival data collection may be accomplished remotely if necessary (i.e., via telephone or electronically), provided these communications are well documented.

If a patient is lost to follow-up or withdraws from the study, survival status will be ascertained through the use of Death Registries, where approved and available (unless the patient withdraws consent from such data collection).

Patients who withdraw consent from the study will be invited to enroll in the OLE study for long-term survival follow-up.

5.3.5 Lung Transplantation

Qualification for lung transplant will be assessed by the investigator. In general, qualification for lung transplant may be regarded as the point in time when a patient would be referred for evaluation for lung transplantation using local guidelines or practice, under ideal circumstances (e.g., no obvious contraindication for lung transplant). When applicable, date of qualification as assessed by investigator will be collected. Date of actual lung transplantation will be collected, when applicable.

5.4 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.3.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.5–5.7.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.3.2 for seriousness criteria), severity (see Section 5.4.3), and causality (see Section 5.4.4).

5.4.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.5.2 for instructions for reporting serious adverse events). *All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, and not on the Adverse Event eCRF.*

After initiation of study drug, all adverse events will be reported until 8 weeks after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.7.

5.4.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.4.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity (see Appendix 9). Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.5.2 for reporting instructions), per the definition of serious adverse event in Section 5.3.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.5.2 for reporting instructions), per the definition of serious adverse event in Section 5.3.2.

5.4.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.4.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.4.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction," or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF.
If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.4.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.4.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.

- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.4.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.5.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.4.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.4.5.4 for details on recording persistent adverse events).

5.4.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.4.5.4 for details on recording persistent adverse events).

5.4.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times ULN$) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times ULN$ in combination with total bilirubin $>2\times ULN$
- Treatment-emergent ALT or AST $>3\times ULN$ in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.4.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.5.2). Any such events should be managed according to local practices and guidelines. No drug-specific management guideline is available, as abnormal liver function tests are not a known adverse drug reaction or risk for PRM-151.

5.4.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.4.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.5.2). This includes death attributed to progression of IPF.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of IPF, "Idiopathic pulmonary fibrosis progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.7.

5.4.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.4.5.10 Lack of Efficacy or Worsening of Idiopathic Pulmonary Fibrosis

Medical occurrences or symptoms of deterioration that are anticipated as part of idiopathic pulmonary fibrosis should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of idiopathic pulmonary fibrosis on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of idiopathic pulmonary fibrosis").

5.4.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.3.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.4.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded

separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2). For PRM-151or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with PRM-*151 or* matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.5 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.3.2; see Section 5.5.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.3.3; see Section 5.5.2 for details on reporting requirements)
- Pregnancies (see Section 5.5.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.5.1 Medical Monitors and Emergency Medical Contacts

In the event of an emergency, the investigator or other physician should use their medical judgment and do what is best for the patient, regardless of protocol requirements. The investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Medical Monitor, in conjunction with the investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and reasons for such deviations must be documented.

Contact Information

Medical Monitor/Emergency Medical Contact:	To be provided by Sponsor
Telephone No.:	To be provided by Sponsor
Mobile Telephone No.:	To be provided by Sponsor
Medical Monitor/Emergency Medical Contact:	To be provided by Sponsor (Secondary)
Telephone No.:	To be provided by Sponsor
Mobile Telephone No.:	To be provided by Sponsor

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.5.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.5.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.5.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 8 weeks after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$8 weeks after the final dose of study treatment are provided in Section 5.7.

5.5.3 Reporting Requirements for Pregnancies

5.5.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 8 weeks after the final dose of study drug.

Female patients *enrolling from site in Japan* of childbearing potential *are prohibited from enrolling in this study. However, in the unlikely event that any female patients enrolling from sites in Japan* become pregnant during the study or within 8 weeks after the final dose of study drug*, they will be instructed to immediately inform the investigator*. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.5.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 8 weeks after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.5.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event,

recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2).

5.6 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.6.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.6.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.7 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 8 weeks after the final dose of study drug), if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either

by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.8 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
PRM-151	PRM-151 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

The suspected unexpected serious adverse reaction (SUSAR) reporting will be as per the national regulatory requirements in participating countries in accordance with the Sponsor’s internal standard operating procedures.

An iDMC will be established to review safety data from this study, thereby better ensuring the safety of study participants. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the iDMC will be constituted of independent clinicians’ expert in the field of IPF and clinical research and a statistician. A formal charter will be established for the conduct of the iDMC. The Committee is planned to review the safety data in an unblinded manner. The iDMC may also review other data (e.g., PK) according to local health authority requirements. *If appropriate, the iDMC may also evaluate benefit and risk by reviewing relevant efficacy data together with safety data during the scheduled iDMC meetings.* Details regarding the iDMC data evaluation will be specified in the iDMC charter.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Unless otherwise specified, all baseline and efficacy analyses will be based on the full analysis set (FAS) defined as all randomized subjects who received at least one administration (full or partial dose) of study drug and will use the grouping as assigned by randomization. The safety evaluable population will include all randomized patients who received at least one administration (full or partial dose) of study drug and will be grouped by treatment received.

The primary analysis will occur when the last enrolled patient has completed the Week 52 study visit. Significance testing of the primary and secondary endpoints will account for multiplicity and control family-wise type I error, which is fixed at 0.05 two-sided. The study has one single primary efficacy endpoint (absolute change from baseline to Week 52 in FVC [mL]) and one family of secondary efficacy endpoints that have been ordered in a prespecified sequence, starting with the key secondary endpoint, absolute change from baseline to Week 52 in 6MWD (see Section 3.3.2). The planned statistical analysis will control the overall type I error for the testing of these efficacy endpoints by applying a fixed-sequence statistical strategy, testing all the endpoints according to the pre-specified order. All hypothesis tests will be two-sided unless otherwise specified.

The SAP will contain full details of the statistical analyses and will be signed before the database lock and prior to any unblinded statistical analyses by the Sponsor. Any change to the planned statistical methods will be documented in the SAP and in the clinical study report.

The global population will include all patients enrolled during the global enrollment phase , and the China subpopulation will include all patients enrolled *in China, Hong Kong and Taiwan* (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subpopulation (see Section 6.12 for information on the China subpopulation analyses).

6.1 PRIMARY EFFICACY ESTIMAND

The primary estimand will evaluate the effectiveness of PRM-151 plus standard of care treatment as needed (excluding lung transplantation) versus matching placebo plus standard of care treatment as needed (excluding lung transplantation). It corresponds to the difference in outcome attributable to the randomized study drug, whatever changes in the treatment regimen (randomized drug and any associated treatment) occurs afterwards (excluding lung transplantation), as described in Mallinckrodt et al. 2017 and Mallinckrodt et al. 2012. Lung transplantation will be handled as a particular intercurrent event (see below). The attributes of the estimand are as follows:

- The treatment regimen of interest is study drug (PRM-151 or placebo) as randomized, in combination with any background or additional treatment (i.e., PRM-151 or placebo taken alone or as an add-on to standard of care with

pirfenidone or nintedanib, dosed as required) including all changes in standard of care treatment and all other additional treatments, with the exclusion of lung transplantation.

- The population is *patients diagnosed with idiopathic pulmonary fibrosis* as defined through the inclusion/exclusion criteria presented in Section 4.1 of the protocol. All patients randomized having received at least one administration (full or partial dose) of the study drug (all treated patients) will be included in the analysis (FAS).
- The variable is the absolute change from baseline to Week 52 in FVC mL for the primary efficacy endpoint.
- The population-level summary measure is the between randomized treatments difference in mean change from baseline at week 52 in FVC mL.
- Intercurrent events (post-randomization events):

  Any change in initial treatment regimen (change in study drug, change in standard of care, use of prohibited medication) will be considered irrelevant in defining the treatment effect of interest. As the primary objective is to assess the effectiveness of PRM-151, the analysis will be performed ignoring any such intercurrent event.

  Deaths are expected to be infrequent as the study plans to include patients with a life expectancy longer than the study duration. Assessments following death will be assigned with values to designate treatment failure. Further details will be provided in the SAP.

  Lung transplantation: Lung transplantation is expected to be rare during the study, as patients likely to receive a lung transplantation during the study are excluded. Any data recorded after lung transplantation will be censored from the analysis because they are no longer an accurate measure of efficacy reflecting the diseased lung(s). In some instances, FVC can improve to over 80% following lung transplantation or even 100% for bilateral lung transplantation 6–12 months after surgery (Hernandez et al. 2018).

Table 5 below summarizes the handling of intercurrent events for the primary efficacy estimand.

Table 5 Primary Efficacy Estimand Analysis Strategy for Intercurrent Events

Intercurrent Event (ICE)		Analysis strategy
Any change to randomized treatment	Temporary study drug discontinuation	Treatment policy All measurements post ICE analyzed
	Permanent study drug discontinuation	
	Temporary or permanent change in study drug dose	
	Missed study drug dose	
	Randomized treatment switches, if any	
Any change in standard of care (SOC), with pirfenidone or nintedanib therapy	SOC started during study	Treatment policy All measurements post ICE analyzed
	Change in dose of SOC	
	SOC discontinued	
	SOC switch (from pirfenidone to nintedanib or vice versa)	
Other concomitant treatment	Use of prohibited concurrent medication (Section 4.4.2)	Treatment policy All measurements post ICE analyzed
Hospitalization for COVID-19		*Treatment policy* *All measurements post ICE analyzed*
Terminal events	Death	No measurements available after such events Composite strategy Assessments following death will be assigned with values to designate treatment failure
	Lung transplantation	Hypothetical strategy Measurements collected after lung transplantation deleted from the analysis Implicit imputation using linear mixed-effect model

ICE = intercurrent event; SOC = standard of care.

6.2 DETERMINATION OF SAMPLE SIZE

The purpose of this study is hypothesis testing regarding the effect of PRM-151 versus placebo.

6.2.1 Assumptions on Treatment Effects for Sample-Size and Power Calculations

The hypotheses on treatment effect-sizes used for sample-size and power calculations were based on the results of the placebo-controlled period of the PRM-151-202 study, summarized in Table 6.

Table 6 Results of the PRM-151-202 Study on Planned Primary and Key Secondary Endpoints

LS-Means for change from baseline to Week 28 (*Linear* Mixed *Effect* Models)				
Endpoint	Placebo (N=39) Mean (SE)	PRM-151 (N=77) Mean (SE)	Difference Mean (SE)	Standardized effect size
FVC (mL)	-242.3 (45.47)	-127.7 (32.86)	114.6 (56.10)	0.40
6MWD (meters)	-33.7 (10.52)	-0.20 (7.59)	33.5 (12.97)	0.51
FVC (% predicted)	-5.40 (0.96)	-2.50 (0.69)	2.80 (1.19)	0.46

6MWD = 6-minute walk distance; FVC = forced vital capacity.

The effect-sizes observed for the between-group differences in least-square means for change from baseline to Week 28 from the linear mixed effect models with random intercept and slope adjusted on stratum, were 114.6 mL for FVC mL (common standard deviation: 286.9, standardized effect-size: 0.40), 33.5 m for 6MWD (common standard deviation: 66.3, standardized effect-size: 0.51), and 2.80% for FVC % predicted (common standard deviation: 6.04, standardized effect-size: 0.46). A greater between group difference is expected at Week 52 in the current study, but a greater variability might also be observed at Week 52, due to the longer follow-up.

In the OLE of the PRM-151-202 study, where all patients received PRM-151 from Week 28 onwards, the Week 52 standard errors from the *Random Coefficient Regression Model (RCRM)* model allowed to compute corresponding standard deviations of 403.5 mL (FVC mL), 8.77% (FVC %predicted) and 82.3 m (6MWD) in patients who were initially randomized to PRM-151, that are indeed larger than those at Week 28 (288.3 mL, 6.06% and 66.6 m respectively).

To avoid underestimating the power of the study and to enable the opportunity to explore the efficacy in relevant patient subgroups including baseline concomitant IPF medication use, smaller standardized effect-sizes than observed in study PRM-151-202 at Week 28 of 0.25 for FVC mL and FVC % predicted and 0.30 for 6MWD were used for the calculations. In addition, to investigate the impact of increased variability for studies of longer duration, the power for this calculated sample size was assessed in the following way: (a) using the placebo-controlled treatment differences observed at Week 28 as estimates for the Week 52 treatment effects and (b) using the Week 52 standard deviations for the initially randomized PRM-151 arm from study PRM-151-202, as

estimates for the Week 52 common standard deviations. This was performed in order to confirm that the nominal power is at least 80% under these assumptions.

With a total of 658 patients (329 in each arm), the nominal power to detect a standardized effect size of 0.25 for FVC mL and FVC % predicted, using a two-sided type I error level of 0.05 is 0.89 and the nominal power to detect a standardized effect size of 0.30 on 6MWD using a two-sided type I error level of 0.05 is 0.97.

With a total of 658 patients (329 in each arm), the nominal power to detect an effect of 114.6 mL on FVC mL with common standard deviation of 403.5 (standardized effect size of 0.28) using a two-sided type I error of 0.05 is 0.95. The nominal power to detect an effect of 33.5 meters on 6MWD with common standard deviation of 82.3 (standardized effect size of 0.41) using a two-sided type I error level of 0.05 is >0.99. For FVC % predicted, the nominal power to detect an effect of 2.80% with common standard deviation of 8.77 (standardized effect size of 0.32) using a two-sided type I error of 0.05 is 0.98.

6.2.1.1 Robustness of Power and Sample-Size Calculations

In Table 7, power calculations for alternative values of the effect-sizes of the $first$ three endpoints in the fixed-$sequence$ testing are provided.

With the planned sample size of 658 patients, a standardized effect-size of 0.220 on FVC, both mL and % predicted (corresponding to absolute between group differences of 89 mL and 1.92%, respectively) will be detected with a power of 80%.

For 6MWD, the study has a high power (0.973) to detect an absolute between group difference of 25 m (considered the minimal clinically relevant difference), corresponding to a standardized effect-size of 0.30. A smaller effect-size of 0.25, corresponding to an absolute difference of 20.8 m will be detected with a power of 90%.

Table 7 Results of Power Calculations for Different Effect-Sizes and N=658 Patients

	alpha	Hypothesized absolute difference	Power with N=658 patients
FVC (mL) H0: difference = 0	0.05 2-sided	114.6	0.953
		107.0	0.925
		102.0	0.899
		95.0	0.854
		89.0	0.806
6MWD (meters) H0: difference = 0	0.05 2-sided	33.5	>0.999
		27.5	0.990
		25.0	0.973
		23.0	0.947
		20.8	0.899
		18.0	0.800
FVC (% predicted) H0: difference = 0	0.05 2-sided	2.80	0.983
		2.45	0.947
		2.33	0.925
		2.22	0.900
		2.05	0.849
		1.92	0.800

Standard deviation of 403.5 mL (FVC mL), 82.3 m (6MWD) and 8.77 (FVC %predicted) based on Week 52 standard errors from the MMRM model in patients who were initially randomized to PRM-151 in Study PRM-151-202.

6MWD = 6-minute walk distance; FVC = forced vital capacity.

6.3 SUMMARIES OF CONDUCT OF STUDY

The number of patients randomized will be tabulated by study site and treatment group. Patient disposition (the number of patients who enroll, discontinue, or complete the study) will be summarized by treatment group. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Unless otherwise specified, the baseline value for each variable will be considered the assessment collected on Treatment Day 1, prior to administration of study drug.

Demographic and baseline characteristics such as age, sex, race/ethnicity, concomitant IPF medication use, comorbid illnesses, and pulmonary function, will be summarized for the FAS population overall and by treatment group using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Exposure to study treatment (number of study drug treatments and duration of treatment) will be summarized overall and by treatment group.

Proportions of patients taking each concomitant medication will be provided.

6.5 EFFICACY ANALYSES

The study endpoints comprise one primary endpoint, one key secondary endpoint, and a series of other secondary endpoints (see Section 2). All the primary and secondary efficacy analyses will be performed on the FAS population. Relying on the analytical strategy presented in Section 6, the planned statistical analysis will control the study-wise type I error at the planned 0.05 two-sided level despite multiple endpoints.

A fixed-sequence testing strategy will be used for statistical testing of first the primary endpoint then the secondary endpoints according to the prespecified order to control the study-wise type I error rate at 0.05 two-sided. See Section 6 for details.

In addition to the analyses described in Sections 6.5.1 and 6.5.2, the following analyses will be performed for the primary efficacy endpoint and key secondary efficacy endpoints. Details of these analyses will be described in the SAP:

- Subgroup analyses to evaluate the consistency of results across prespecified subgroups (e.g., concurrent use of IPF treatment, geographic region*, first and second generation PRM-151*)

6.5.1 Primary Efficacy Analysis

All FVC mL measurements that meet the minimal level of quality will be used for this analysis, except those recorded after lung transplantation, whatever other intercurrent events might have occurred before that were recorded. Assessments following death will be assigned with values to designate treatment failure, and the details will be provided in the SAP.

The comparison of PRM-151 with placebo will be carried out via a two-sided statistical test. The primary efficacy endpoint will be analyzed using a linear mixed-effect model with random intercept and random slope, with FVC mL measured at each timepoint as *the* dependent variable, stratification factors, age, sex, height and treatment by time interaction as fixed effects, and subject and time as random effects. The random intercept represents deviations from the mean baseline FVC mL measure for each subject. The model will assume an unstructured covariance structure. If there are convergence problems with the model, the following covariance structures will be tested: compound symmetry, first-order autoregressive [AR(1)] and Toeplitz. The covariance

structure converging to the best fit, based on Akaike's information criterion (AIC), will be used.

The comparison of PRM-151 with placebo will be carried out by computing the estimate of the difference in absolute change from baseline at Week 52 between the two treatment arms with 95% CIs and p-value.

6.5.2 Key Secondary Efficacy Endpoint

If the primary efficacy test on FVC mL is found significant at the alpha level of 0.05 two-sided then the fixed sequence testing procedure will continue by testing 6MWD at the alpha level of 0.05 two-sided.

The key secondary endpoint (6MWT) will be analyzed using the same methodology as the primary endpoint with specifics for models and summaries detailed in the SAP.

6.5.3 Analyses Addressing the Effect of Missing Data

All efforts will be made to minimize missing data. Assessments following *death and lung transplantation will be imputed for the* primary and key secondary endpoints*. No other* imputation *for missing* data is *planned to be performed for the primary analysis, as the planned analysis model* is *capable of handling missing data when the data are assumed to be missing at random (MAR). Various* sensitivity *analyses to support the primary analysis will use alternative methods of handling missing values. Details* will be provided in the SAP

6.5.4 Other Secondary Efficacy Analyses

As mentioned in Section 6.5, and conditional to significant results being obtained first on the primary endpoint and then the key secondary endpoint, the remaining secondary endpoints will be tested using the fixed-sequence strategy in the predefined order presented in Section 2.1.2, each at the same significance level of 0.05 two-sided and the testing sequence will stop as soon as a non-significant result is observed.

In case a non-significant test occurs during this testing sequence, the tests for the remaining endpoints in the sequence will nevertheless be computed as sensitivity/exploratory analyses but will not allow any formal claim of efficacy on these endpoints.

All continuous secondary endpoints will be analyzed using the same methodology as the primary endpoint. The SAP will detail specifics for models and summaries.

For time to event endpoints, the log-rank test will be used for the comparison between the two treatment arms. The hazard ratio will be estimated using a Cox regression model. Descriptive statistics and Kaplan-Meier curves will be provided. Details on model specifications will be provided in the SAP.

6.5.5 Exploratory Efficacy Analyses

Exploratory efficacy analyses will be described in detail in the SAP.

6.6 SAFETY ANALYSES

Safety analyses will consist of all randomized patients who received at least one administration (full or partial dose) of study drug, with patients grouped according to treatment received. Safety summaries will be presented by treatment arm for all treated patients. *Details of supplemental subgroup analyses comparing the safety of first and second generation PRM-151 will be provided in the SAP.*

Safety will be assessed through summaries of exposure to study treatment, adverse events, *SAEs, AESIs,* and changes in laboratory test results.

6.6.1 Analyses of Exposure, Adverse Event, and Laboratory Data

Study treatment exposure (such as treatment duration, total dose received) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped using the most current version of the MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 scale. A by-patient adverse event data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, timing from first and last dose of PRM-151, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade.

6.7 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to determine concentrations of PRM-151 at specified timepoints, unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred which may interfere with PK evaluation, with patients grouped according to treatment received.

Individual and mean PRM-151 concentration versus time data will be tabulated and summarized descriptively. The pharmacokinetics of PRM-151 will be summarized by one or more key PK parameters (as appropriate for data collected). Estimates for these

parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

Additional exploratory PK analyses will be conducted as appropriate.

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned. *Supplemental subgroup analyses will be performed to compare first and second generation PRM-151.*

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy and PK, may be analyzed and reported via descriptive statistics.

6.9 BIOMARKER ANALYSES

Biomarkers will be assessed at baseline and subsequent timepoints following administration of PRM-151. Biomarkers will be presented as absolute value over time and/or percent change relative to baseline over time. Biomarker levels at baseline or over time may be compared with efficacy or safety measurements to assess prognostic or predictive properties. Samples taken during screening and baseline before first PRM-151 dose may be averaged to better normalize postdose endpoints taking into account normal variability.

Genetic assessments may include genotype-outcome comparisons to assess prognostic or predictive properties.

Descriptive or summary statistics will be used to describe biomarker and genetic assessments.

6.10 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

6.11 *INTERIM ANALYSES*

6.11.1 *Planned Interim Analysis*

An interim futility analysis will be performed after at least 40% of patients have completed their Week 28 visits. *The futility boundary for this analysis is calculated to correspond approximately to 25% Bayesian Predictive Power, assuming a linear extrapolation between Week 28* and Week 52 visits.

This interim futility analysis will be conducted by an external statistical group and reviewed by the iDMC. *The Sponsor will remain blinded. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.*

The details regarding this futility analysis will be documented in the SAP and *will be submitted to FDA at least 2 months prior to the conduct of the interim analysis. The SAP may also be submitted to other health authorities upon request. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the futility analysis (e.g., stop the study for futility, continue the study), and the iDMC charter will be made available to health authorities upon request.*

6.11.2 Optional Interim Analysis

No *other* efficacy interim analyses are planned at this time. However, in exceptional circumstances, when patient enrollment and study conduct is significantly impacted by external factors such that study completion does not seem feasible (e.g., ongoing or worsening impact of the global COVID-19 pandemic, the availability of compelling clinical trial results for an external competitor molecule, or significant changes in standard of care), the Sponsor may choose to conduct one interim efficacy analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim *efficacy* analysis is conducted, the Sponsor will remain blinded. The interim *efficacy* analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter. If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

6.12 CHINA SUBPOPULATION ANALYSES

The China subpopulation will include all patients enrolled *in China, Hong Kong and Taiwan* (i.e., during both the global enrollment phase and the extended China enrollment phase). Results from these analyses will be summarized in a separate Clinical Study Report.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data, spirometry, HRCT, DLCO and other non-eCRF data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-

related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO and clinician-reported outcome data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC−approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S.

Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will

be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor or delegate contract research organization (CRO) will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor or CRO will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This study is sponsored and managed by F. Hoffmann-La Roche Ltd. A CRO will manage clinical site operations and medical monitoring.

Approximately 400 sites globally will participate to enroll approximately 658 patients. An IxRS will be used for study drug inventory management and to enroll patients in this study.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses, PFTs), as specified in Section 4.5.

Samples for urine pregnancy tests will be analyzed at site locally. Samples for PD, PK, biomarker, and ADA tests will be sent to the Sponsor or a designee for storage and analysis.

PRO data will be recorded electronically via devices supplied by a PRO vendor.

HRCT imaging and lung biopsy slides (if available) will be read centrally and managed by a central reading vendor(s).

An iDMC will be employed to monitor and evaluate patient safety throughout the study. The iDMC may also monitor other data (e.g., PK). Details regarding the iDMC data evaluation and monitoring will be specified in the iDMC charter.

A Clinical Adjudication Committee, an independent and blinded expert clinician panel, will adjudicate potential cases of acute exacerbations of IPF, hospitalizations for respiratory causes and all deaths. The definition of events for independent assessment, criteria for adjudication of events and details of the adjudication process will be provided in a charter. The clinical expert panel's composition and a description of its responsibilities will also be provided in the charter.

An Anaphylaxis Adjudication Committee, an independent and blinded committee composed of external experts in allergic diseases, will adjudicate all potential anaphylaxis cases reported by investigators to the Sponsor. The committee will assess whether the reported event is a true anaphylaxis event (based on Sampson's criteria) and whether the reported anaphylaxis event is causally related to study treatment. Further details will be provided in the Anaphylaxis Adjudication Charter.

An external global Steering Committee, comprised of recognized experts in IPF, will provide oversight of Study WA42293 and Study WA42294. Their roles and responsibilities will be outlined in the Steering Committee Charter.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: Guidelines for the six-minute walk test. Am J Respir And Crit Care Med 2002;166:111–7.

Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: A systematic review. J Eval Clin Pract 2016;23:377–81.

Brooks. 1996. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Brown AW, Nathan SD. The value and application of the 6-minute-walk test in idiopathic pulmonary fibrosis. Ann Am Thorac Soc. 2018;15:3–10.

Caminati A, Bianchi A, Cassandro R, et al. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. Respir Med 2009;103:117–23.

Castano A, Lin SL, Surowy T, et al. Serum amyloid P inhibits fibrosis through Fc gamma R-dependent monocyte/macrophage regulation in vivo. Science Translational Medicine 2009;1:5ra13.

Collard HR, King TE, Bucher Bartelson B, et al. 2003. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:538–42.

Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med 2016;194:265–75.

Cox N, Pilling D, Gomer RH. Serum amyloid P: A systemic regulator of the innate immune response. J Leukoc Biol 2014:96;739–43.

De Biasi S, Cerri S, Bianchini E, et al. Levels of circulating endothelial cells are low in idiopathic pulmonary fibrosis and are further reduced by anti-fibrotic treatments. BMC Med 2015;13:277.

DeMets DL, Lan G. Interim analysis: the alpha spending function approach. Stat Med1994;13:1341–52.

Dillingh MR, van den Blink B, Moerland M, et al. Recombinant human serum amyloid P in healthy volunteers and patients with pulmonary fibrosis. Pulm Pharmacol Ther 2013;26:672–6.

Dressen A, Abbas AR, Cabanski C, et al. Analysis of protein-altering variants in telomerase genes and their association with MUC5B common variant status in patients with idiopathic pulmonary fibrosis: A candidate gene sequencing study. Lancet Respir Med 2018;6:603–14.

du Bois RM, Albera C., Bradford WZ, et al. 6-Minute walk distance is an independent predictor of mortality in patients with idiopathic pulmonary fibrosis. Eur Respir J 2014;43:1421–9.

du Bois RM, Weycker D, Albera C, et al. Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. Am J of Respir Crit Care Med 2011;183:1231–7.

Eaton T, Young P, Milne D, et al. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005;171:1150–7.

EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life Health Policy 1990;16:199–208.

FDA Guidance for Industry 2006. U.S. Food and Drug Administration. Guidance for clinical trial sponsors: establishment and operation of clinical trial data monitoring [resource on the internet]. 2006 [cited: 12 March 2020]. Available from: https://www.gmp-compliance.org/guidelines/gmp-guideline/fda-guidance-for-clinicaltrial-sponsorson-the-establishment-and-operationof-clinical-trial-data-monitoringcommittees.

[FDA] U.S. Food and Drug Administration. Table of surrogate endpoints that were the basis of drug approval or licensure [resource on the Internet]. 2018 [updated: 30 September 2019, cited: 12 March 2020]. Available from: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.

Flaherty KR, Andrei AC, Murray S, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 2006;174:803–9.

Frankel SK, Schwarz M. Update in idiopathic pulmonary fibrosis. Curr Opin Pulm Med 2009;15:463–9.

Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30:2493–537.

Garlanda C, Bottazzi B, Bastone A, et al. Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. Annu Rev Immunol 2005;23:337–66.

Gewurz H, Zhang XH, Lint TF. Structure and function of the pentraxins. Curr Opin Immunol 1995;7:54–64.

Haudek SB, Xia Y, Heubener P, et al. Bone marrow-derived fibroblast precursors mediate ischemic cardiomyopathy in mice. Proc Natl Acad Sci U S A 2006;103:18284–9.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research 2011;20:1727–36.

Hernandez RL, Perez MA, Carrasco MT, et al. Lung transplantation in idiopathic pulmonary fibrosis. Med Sci 2018;6:68.

Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1428–46.

Hutchinson J, Fogarty A, Hubbard R, et al. Global incidence and mortality of idiopathic pulmonary fibrosis: a systemic review. Eur Respir J 2015;46:795–806.

ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials – Step 2 (resource on the Internet). 16 June 2017 [cited: 12 March 2020]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Quality of Life Research 2013;22:1717–27.

Ji Z, Ke ZJ, and Geng JG. SAP suppresses the development of experimental autoimmune encephalomyelitis in C57BL/6 mice. Immunol Cell Biol. 2011;90:388–95. doi: 10.1038/icb.2011.51. Epub 2011 Jun 7.

Jo HE, Glaspole I, Moodley Y, et al. Disease progression in idiopathic pulmonary fibrosis with mild physiological impairment: Analysis from the Australian IPF registry. BMC Pulm Med 2018;18:19.

Jones PW, Quirk FH, Baveystock CM, et al. 1992. A Self-complete Measure of Health Status for Chronic Airflow Limitation. The St. George's Respiratory Questionnaire Am Rev Respir Dis 1992;145:1321–7

King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083–92.

Lederer DJ, Arcasoy SM, Wilt JS, et al. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006;174:659–64.

Lettieri CJ, Nathan SD, Barnett SD, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006;129:746–52.

Lupher ML Jr, Gallatin WM. Regulation of fibrosis by the immune system. Adv Immunol 2006;89:245–88.

Mallinckrodt C, Lin Q, Lipkovich I, et al. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharmaceut Statist 2012;11:456–61.

Mallinckrodt C., Molenberghs G, and Rathmann S. Choosing estimands in clinical trials with missing data. Pharmaceut Statist 2017;16:29–36.

Mantovani A, Garlanda C, Doni A, et al. Pentraxins in innate immunity: From C-reactive protein to the long pentraxin PTX3. J Clin Immunol 2008;28:1–13.

Moeller A, Gilpin SE, Ask K, et al. Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2009;179:588–94.

Moreira AP, Cavassani KA, Hullinger R, et al. Serum amyloid P attenuates M2 macrophage activation and protects against fungal spore-induced allergic airway disease. J Allergy Clin Immunol 2010;126:712–721.

Murray LA, Chen Q, Kramer MS, et al. TGF-beta driven lung fibrosis is macrophage dependent and blocked by Serum amyloid P. Int J Biochem Cell Biol 2011;43:154–62.

Murray LA, Rosada R, Moreira AP, et al. Serum amyloid P therapeutically attenuates murine bleomycin-induced pulmonary fibrosis via its effects on macrophages. PLoS One 2010;5:e9683.

Naik-Mathuria B, Pilling D, Crawford JR, et al. Serum amyloid P inhibits dermal wound healing. Wound Repair Regen 2008;16:266–273.

Nathan SD, Albera C, Bradford WZ, et al. Effect of continued treatment with pirfenidone following clinically meaningful declines in forced vital capacity: Analysis of data from three phase 3 trials in patients with idiopathic pulmonary fibrosis. Thorax 2016;71:429–35.

Nathan SD, Du Bois RM, Albera C, et al. 6-Minute walk test (6MWT) in patients with idiopathic pulmonary fibrosis (IPF): Confirmation of test performance characteristics [abstract]. Am Thorac Soc 2013; abstract 2360.

Nathan SD, Du Bois RM, Albera C, et al. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respir Med. 2015;109:914–22.

Nathan SD, Meyer KC. IPF clinical trial design and endpoints. Curr Opin Pulm Med 2014;20:463–71.

Neighbors M, Cabanski CR, Ramalingam TR, et al. Prognostic and predictive biomarkers for patients with idiopathic pulmonary fibrosis treated with pirfenidone: Post-hoc assessment of the CAPACITY and ASCEND trials. Lancet Respir Med 2018;6:615–26.

Nintedanib [package insert]. Boeringher-Ingerlheim; 2019.

Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med 2007;176:277–84.

Pepys MB, Booth DR, Hutchinson WL, et al. Amyloid P component. A critical review. Amyloid 1997;4:274–95.

Pilling D, Roife D, Wang M, et al. Reduction of bleomycin-induced pulmonary fibrosis by serum amyloid P. J Immunol 2007;179:4035–44.

Pirfenidone [package insert]. Genentech; 2019.

Popescu F-D, Cristea OM, Ionica F-E, et al. Drug allergies due to IgE sensitization to a-Gal. Farmacia 2019; 67:43–8.

Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788–824.

Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018;199:A2636.

Raghu G, van den Blink B, Hamblin MJ, et al. Long-Term Safety and Efficacy of Recombinant Human Pentraxin-2 in Patients with Idiopathic Pulmonary Fibrosis Am J Respir Crit Care Med 2019;200:1089–92.

Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of idiopathic pulmonary fibrosis. An update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med 2015;192:e3–19.

Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet 2017;389:1941–52.

Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071–82.

Sampson HA, Munoz-Furlong A, Campbell RL, et al: Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117: 391–7.

Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: Measurement

properties of field walking tests in chronic respiratory disease. Eur Respir J 2014;44:1447–78.

Saketkoo LA, Mittoo S, Huscher D, et al. Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials. Thorax 2014;69:428–36.

Steel DM, Whitehead AS. The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. Immunol Today 1994;15:81–8.

Swigris JJ, Wamboldt FS, Behr J, et al. The six-minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference. Thorax 2010;65:173–7.

van den Blink B, Dillingh MR, Ginns LC, et al. Recombinant human pentraxin-2 therapy in patients with idiopathic pulmonary fibrosis: safety, pharmacokinetics and exploratory efficacy. Eur Respir J 2016;47:889–897.

Verma G, Marras T, Chowdhury N, et al. Health-related quality of life and 6 min walk distance in patients with idiopathic pulmonary fibrosis. Can Respir J 2011;18:283–7.

Wolters PJ, Blackwell TS, Eickelberg O, et al. Time for a change: Is idiopathic pulmonary fibrosis still idiopathic and only fibrotic? Lancet Respir Med 2018;6:154–60.

Zhang W, Wu J, Qiao B, et al. Amelioration of lupus nephritis by serum amyloid p component gene therapy with distinct mechanisms varied from different stage of the disease. PLoS One 2011;6:e22659.

Appendix 1
Schedule of Activities

Assessment	Screening Period [a]	Baseline/ Dosing Day 1	Dosing Day 3	Dosing Day 5	Week														Treat. Discon. Visit [d]	Study Discon. Visit [d]
					4	8	12	16	20	24	28	32	36	40	44	48	52 [b]	56 [c]		
Window	**4 weeks**	Loading within 8 days [e]			(± 5 days) [f]															
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**		
Informed consent	x																			
Demographics	x																			
Medical history	x																			
Inclusion/Exclusion	x	x																		
Height (cm)	x																			
Pregnancy test (serum pregnancy analyzed at central lab)-*WOCBP only*	x																			
TB test [g]	x																			
SAFETY ASSESSMENTS																				
Vital signs [h]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Physical exam [i]	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight (kg)	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x			
AE/SAE assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior/Concomitant medications and oxygen use	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x									x							x		x	

Appendix 1: Schedule of Activities

Assessment	Screening Period [a]	Baseline/ Dosing Day 1	Dosing Day 3	Dosing Day 5	Week														Treat. Discon. Visit [d]	Study Discon. Visit [d]
					4	8	12	16	20	24	28	32	36	40	44	48	52 [b]	56 [c]		
Window	**4 Weeks**	Loading within 8 days [e]			(± 5 days) [f]															
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**		
LABORATORY ASSESSMENTS																				
Blood tests (hematology, chemistry, coagulation)	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SARS-CoV-2 serology [j]		x					x			x			x				x		x	
Urine pregnancy test (*WOCBP* only)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis	x	x					x			x			x				x		x	
Serum tryptase, ADA sample, complement C3, *PK* for *≥ Grade 2* infusion-related reactions or suspected anaphylaxis *or hypersensitivity reactions* [k]	x																			
PK, PD, and ADA sampling [l]	See Appendix 2, Appendix 3, and Appendix 4.																			

Appendix 1: Schedule of Activities

Assessment	Screening Period [a]	Baseline/ Dosing Day 1	Dosing Day 3	Dosing Day 5	Week														Treat. Discon. Visit [d]	Study Discon. Visit [d]
					4	8	12	16	20	24	28	32	36	40	44	48	52 [b]	56 [c]		
Window	4 Weeks	Loading within 8 days [e]			(± 5 days) [f]															
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
EFFICACY ASSESSMENTS																				
Healthcare utilization for respiratory events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Assessment of IPF exacerbations and hospitalizations		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Spirometry	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x		x	
6-minute walk test and Borg Scale	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x		x	
DLCO	x	x					x			x			x				x		x	
Patient reported outcomes: SGRQ, UCSD-SOBQ, and EQ-5D-5L [m]		x					x			x			x				x		x	
HRCT [n]	x																x			
TREATMENT ASSESSMENTS																				
Study drug dosing [o, p]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Adherence to pirfenidone or nintedanib [q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Lung transplantation assessment	x																			

ADA = anti-drug antibody; AE = adverse event; Discon. = discontinuation; DLCO = diffusing capacity for carbon monoxide; eCRF = electronic Case Report Form; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; OLE = open-label extension; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; SGRQ = St. George Respiratory Questionnaire; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis; Treat. = treatment, UCSD-SOBQ = University of California, San Diego-Shortness of Breath Questionnaire.

[a] Screening period is up to 4 weeks. Eligible patients can be randomized as soon as their screening assessments have been completed and all eligibility criteria have been confirmed. Randomization must occur prior to any baseline assessments being conducted on Visit 2.

[b] Patients will have their final safety and efficacy assessments, including HRCT if applicable, at Week 52.

[c] Patients not enrolling in the OLE study will return for an end-of-study visit at Week 56.

[d] Treatment discontinuation visit should occur 4 weeks after final dose of study drug. Study discontinuation visit should occur 4 weeks after the treatment discontinuation visit (8 weeks after the final dose of study drug).

[e] To allow for flexibility around weekends, holidays, and so on, the loading dose visits may occur over a time span of up to 8 days, with a minimum of 1 full calendar day between administration of doses (patients must not be dosed on consecutive days). In case one or more loading doses have been missed or delayed beyond the 8-day loading phase window, loading doses should be administered again at the next scheduled visit. No loading doses should be administered outside of the 8-day loading phase window.

[f] Patients who discontinue study drug early will have ± 2-week window to complete study visits.

[g] Testing for active or latent TB should be conducted with an interferon gamma release assay during screening. Patients who have completed treatment for active or latent tuberculosis within 6 months prior to screening, and have no evidence of recurrent disease, do not need to be tested.

[h] On dosing days, vital signs should be completed predose (within 60 minutes prior to dosing), every 15 minutes during infusion, and 30–60 minutes postdose.

[i] Full physical exam during screening and baseline, and an abbreviated physical exam thereafter.

[j] Patients will have an assessment for SARS-CoV-2 serology at baseline, then every 3 months, and at the Week 52 visit. In the event of an acute respiratory exacerbation or infection during the study, additional SARS-CoV-2 serology or PCR testing may be performed according to local guidelines as needed.

[k] *Blood samples for ADA, serum tryptase, complement C3, and PK analyses should be obtained at the time of the events of ≥ Grade 2 infusion-related reactions, or suspected anaphylaxis, or hypersensitivity reactions whenever possible. Serum tryptase should be collected between 1 and 6 hours after the event and a b*lood sample for ADA, serum tryptase, complement C3, should be obtained at the first follow-up visit after the events of suspected anaphylaxis, or hypersensitivity reactions.

[l] For PK, /PD *biomarker* and ADA sampling schedule, see Appendix 2. For China-specific schedule, see Appendix 3. *For Japan-specific schedule, see Appendix 4.*

[m] SGRQ, UCSD-SOBQ, and EQ-5D-5L are to be completed in this order and prior to any other trial-related procedures.

[n] If an HRCT of adequate quality for confirmation of eligibility is not available within 12 months prior to screening, an HRCT must be obtained during screening for eligibility verification. Only patients who have HRCT performed as part of screening are required to have a repeat HRCT scan at Week 52.

[o] Repeat loading doses will be required if patients miss infusions of study treatment. Following a missed infusion, the patient should receive three doses on alternate days at the next scheduled visit; scheduled efficacy assessments will only be performed on the first of the three loading dose days. Additional PK/PD samples may be taken in such cases (see Appendix 2, unscheduled visits).

[p] In exceptional circumstances, if the site is unable to perform all study procedures on the same day or at the same site, study drug infusion may be administered up to 48 hours after the on-site efficacy assessments, provided that these are completed within the 5-day visit window. However, the sequence of procedures must be maintained, and all efforts should be made to complete study assessments and procedures on the same date.

[q] At each visit, the investigator should assess the patient's use of pirfenidone or nintedanib since the last visit. Any change in dose should be recorded on the eCRF.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for all IPF Patients, Excluding China*, *Hong Kong*, *Taiwan*, and Japan*

Visit	Timepoint	Window	Sample Type [a]	Optional Biomarker Sample
Screening	NA		PRM-151 PD biomarker (serum, plasma, Paxgene for RNA, and DNA [b])	RBR DNA [b] PBMCs [c] Urine [d]
Day 1	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [e]	Urine [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [e]	PBMCs [c]
			PRM-151 PD biomarker (serum, plasma and Paxgene for RNA)	
Day 5	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [e]	Urine [d]
			PRM-151 PD biomarker (serum and plasma)	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [e]	PBMCs [c]
			PRM-151 PD biomarker (serum, plasma and Paxgene for RNA)	
Week 4	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [e]	Urine [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [e]	PBMCs [c]
			PRM-151 PD biomarker (serum, plasma and Paxgene for RNA)	
Week 12	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [e]	Urine [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [e]	PBMCs [c]
			PRM-151 PD biomarker (serum, plasma and Paxgene for RNA)	

Appendix 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for all IPF Patients, Excluding China

Visit	Timepoint	Window	Sample Type [a]	Optional Biomarker Sample
Week 24	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [e]	Urine [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
Week 36	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK [e]*	*Urine [d]*
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
Week 48	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [e]	Urine [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
Week 52 or treatment discontinuation visit and Week 56 and unscheduled visits [f]	NA	NA	PRM-151 PK [e]	NA
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	

ADA = anti-drug antibody; IPF = idiopathic pulmonary fibrosis; NA = not applicable; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic; RBR = Research Biosample Repository; WGS = whole genome sequencing.

**Note: Once sufficient numbers of patients enrolling from China, Hong Kong and Taiwain is met, as determined by emerging PRM-151 PK data, patients enrolling from these countries will follow the schedule as specified in Appendix 2.*

[a] Blood draws for PK/ADA/PD biomarker samples must be taken from the opposite arm from study drug administration.

[b] DNA for genetic analyses may include telomere length measurement and WGS. Mandatory DNA collections are contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee and, if applicable, an appropriate regulatory body. If mandatory collection is not approved, the RBR DNA sample should be collected only from patients that have given specific consent (Consent of Optional Collection and/or Storage of Samples for the Research Biosample Repository) to participate in optional research instead. If a DNA sample is not collected during screening, it may be collected at any other visit.

[c] The PBMC samples are optional and should be obtained only from patients who sign the separate RBR Informed Consent Form.

Appendix 2: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for all IPF Patients, Excluding China

[d] The urine samples are optional and should be obtained only from patients who sign the separate RBR Informed Consent Form to collect residual samples at assigned clinical visits.

[e] PK samples will be collected as plasma, and ADA samples will be collected as serum.

[f] If starting the extension study at Week 52, PRM-151 PK, ADA, and PD biomarker samples should be collected prior to dosing. In circumstances when drug reloading is required, if the first day of the start of reloading does not coincide with the planned sample collection dates, PK, ADA, and PD biomarker samples should be taken prior to the start of the first loading dose.

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for IPF Patients in China, Hong Kong and Taiwan

Visit	Timepoint	Window	Sample Type [a]
Screening	NA		PRM-151 PD biomarker (serum and plasma) [b]
Day 1	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
			PRM-151 ADA [c]
	1 hour after the start of IV infusion (i.e., immediately after the end of infusion)	+15 min	PRM-151 PK [c]
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
	4 hours after the start of IV infusion	±15 min	PRM-151 PK [c]
	8 hours after the start of IV infusion	±15 min	PRM-151 PK [c]
	12 hours after the start of IV infusion	±30 min	PRM-151 PK [c]
	24 hours after the start of IV infusion	±30 min	PRM-151 PK [c]
Day 3	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [c]
Day 5	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
Week 4	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
			PRM-151 ADA [c]
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)

Appendix 3: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for IPF Patients in China, Hong Kong and Taiwan

Visit	Timepoint	Window	Sample Type [a]
Week 12	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
			PRM-151 ADA [c]
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
Week 24	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
			PRM-151 ADA [c]
Week 36	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK [c]*
			PRM-151 PD biomarker (serum and plasma)
			PRM-151 ADA [c]
Week *48*	Prior to the start of IV infusion	–2 to 0 hours	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
			PRM-151 ADA [c]
Week 52 or treatment discontinuation visit and Week 56 and *unscheduled* visits [d]	NA	NA	PRM-151 PK [c]
			PRM-151 PD biomarker (serum and plasma)
			PRM-151 ADA [c]

ADA = anti-drug antibody; HGRAC = Human Genetics Resources Administration of China; IPF = idiopathic pulmonary fibrosis; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic.

Note: Once sufficient numbers of patients enrolling from China, Hong Kong and Taiwain is met, as determined by emerging PRM-151 PK data, patients enrolling from these countries will follow the schedule as specified in Appendix 2.

[a] PRM-151 PK, PD biomarker, and ADA sample collection, testing, data export, and data sharing must follow local HGRAC policy. Blood draws for PK/ADA/PD biomarker samples must be taken from the opposite arm from study drug administration.

[b] For those IPF patients enrolled in China, PRM-151 PD biomarker samples will be measured only for the following protein biomarkers: CCL18, OPN, YKL40, and CXCL13, which are all macrophage-derived products implicated in IPF disease (Neighbors M, Cabanski CR, Ramalingam TR, et al. Prognostic and predictive biomarkers for patients with idiopathic pulmonary fibrosis treated with pirfenidone: post-hoc assessment of the CAPACITY and ASCEND trials. Lancet Respir Med 2018;6:615–26). Longitudinal measurements are collected to assess PRM-151 PD activity on the protein biomarker levels.

[c] PK samples will be collected as plasma, and ADA samples will be collected as serum.

[d] If starting the extension study at Week 52, PRM-151 PK, ADA, and PD biomarker samples should be collected prior to dosing. In circumstances when drug reloading is required, if the first day of the start of reloading does not coincide with the planned sample collection dates, PK, ADA, and PD biomarker samples should be taken prior to the start of the first loading dose.

Appendix 4 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for IPF Patients in Japan

Visit	*Timepoint*	*Window*	*Sample Type* [a]	*Optional Biomarker Sample*
Screening	*NA*	*NA*	*PRM-151 PD biomarker (serum, plasma, Paxgene for RNA, and DNA* [b]*)*	*RBR DNA* [b] *PBMCs* [c] *Urine* [d]
Day 1	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK* [e]	*Urine* [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
	1 hour after the start of IV infusion (i.e., immediately after the end of infusion)	*+ 15 min*	*PRM-151 PK* [e]	*NA*
	2 hours after the start of IV infusion	*± 15 min*	*PRM-151 PK* [e]	*PBMCs* [c]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	
	4 hours after the start of IV infusion	*± 15 min*	*PRM-151 PK* [e]	*NA*
	10 hours after the start of IV infusion	*± 2 hours*	*PRM-151 PK* [e]	*NA*
	24 hours after the start of IV infusion	*± 30 min*	*PRM-151 PK* [e]	*NA*
Day 3	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK* [e]	*NA*
Day 5	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK e*	*Urine* [d]
			PRM-151 PD biomarker (serum and plasma)	
	2 hours after the start of IV infusion	*± 15 min*	*PRM-151 PK* [e]	*PBMCs* [c]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	
Week 4	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK* [e]	*Urine* [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
	2 hours after the start of IV infusion	*± 15 min*	*PRM-151 PK* [e]	*PBMCs* [c]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	

Appendix 4: Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for IPF Patients in Japan

Visit	*Timepoint*	*Window*	*Sample Type* [a]	*Optional Biomarker Sample*
Week 12	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK* [e]	*Urine* [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
	2 hours after the start of IV infusion	*± 15 min*	*PRM-151 PK* [e]	*PBMCs* [c]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	
Week 24	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK* [e]	*Urine* [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
Week 36	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK* [e]	*Urine* [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
Week 48	*Prior to the start of IV infusion*	*–2 to 0 hours*	*PRM-151 PK* [e]	*Urine* [d]
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	
Week 52 or treatment discontinuation visit and Week 56 and unscheduled visits [f]	*NA*	*NA*	*PRM-151 PK* [e]	*NA*
			PRM-151 PD biomarker (serum and plasma)	
			PRM-151 ADA [e]	

ADA = anti-drug antibody; IPF = idiopathic pulmonary fibrosis; NA = not applicable; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic; RBR = Research Biosample Repository; WGS = whole genome sequencing.

a Blood draws for PK/ADA/PD biomarker samples must be taken from the opposite arm from study drug administration.

b DNA for genetic analyses may include telomere length measurement and WGS. Mandatory RBR DNA collections are contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee and, if applicable, an appropriate regulatory body. If mandatory collection is not approved, the RBR DNA sample should be collected only from patients that have given specific consent (Consent of Optional Collection and/or Storage of Samples for the Research Biosample Repository) to participate in optional research instead. If a DNA sample is not collected during screening, it may be collected at any other visit.

c The PBMC samples are optional and should be obtained only from patients who sign the separate RBR Informed Consent Form.

d The urine samples are optional and should be obtained only from patients who sign the separate RBR Informed Consent Form to collect residual samples at assigned clinical visits.

e PK samples will be collected as plasma, and ADA samples will be collected as serum.

f If starting the extension study at Week 52, PRM-151 PK, ADA, and PD biomarker samples should be collected prior to dosing. In circumstances when drug reloading is required, if the first day of the start of reloading does not coincide with the planned sample collection dates, PK, ADA, and PD biomarker samples should be taken prior to the start of the first loading dose.

Appendix 5
Sampson's Criteria for Diagnosing Potential Cases of Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

   b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

REFERENCE

Sampson HA, Munoz-Furlong A, Campbell RL, et al: Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117: 391–7.

Appendix 6
St. George's Respiratory Questionnaire

<u>Do not reproduce or distribute</u>. The Sponsor will provide sites with all instruments to be completed in this study.

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problems ☐

If you have ever held a job:

Please check (✓) *one*:

- My respiratory problems made me stop working altogether ☐
- My respiratory problems interfere with my job or made me change my job ☐
- My respiratory problems do not affect my job ☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

For each statement please check (✓) ***the box*** that applies to you ***these days***:

	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

continued…

Appendix 6: St. George's Respiratory Questionnaire

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

For each statement, please check (✓) ***the box*** that applies to you ***because of your respiratory problems***:

	True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

Appendix 6: St. George's Respiratory Questionnaire

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

.....

.....

.....

.....

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

Appendix 7
University of California, San Diego – Shortness of Breath Questionnaire

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

UCSD MEDICAL CENTER
PULMONARY REHABILITATION PROGRAM
SHORTNESS-OF-BREATH QUESTIONNAIRE

Please rate the breathlessness you experience when you do, or if you were to do, each of the following tasks. **Do not skip any items.** If you've never performed a task, or no longer perform it, give your best estimate of the breathlessness you would experience while doing that activity. Please review the two sample questions below before turning the page to begin the questionnaire.

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximum or unable to do because of breathlessness

1. Brushing my teeth.....0 1 2 ③ 4 5

Harry has felt moderately short of breath during the past 7 days while brushing his teeth and so circles a three for this activity.

2. Mowing the lawn.....0 1 2 3 4 ⑤

Anne has never mowed the lawn before but estimates that she would have been too breathless to do this activity during the past 7 days. She circles a five for this activity.

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When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximum or unable to do because of breathlessness

1.	At rest	0	1	2	3	4	5
2.	Walking on a level at my own pace	0	1	2	3	4	5
3.	Walking on a level with others my age	0	1	2	3	4	5
4.	Walking up a hill	0	1	2	3	4	5
5.	Walking up stairs	0	1	2	3	4	5
6.	While eating	0	1	2	3	4	5
7.	Standing up from a chair	0	1	2	3	4	5
8.	Brushing my teeth	0	1	2	3	4	5
9.	Shaving and/or brushing my hair	0	1	2	3	4	5
10.	Showering/bathing	0	1	2	3	4	5

SOBQ - United Kingdom/English - Version of 23 Feb 11 - Mapi Research Institute.
ID5977 / SOBQ_AU1.0_eng-GB.doc

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0	None at all
1	
2	
3	
4	Severe
5	Maximum or unable to do because of breathlessness

11.	Dressing	0	1	2	3	4	5
12.	Picking things up and tidying up a room	0	1	2	3	4	5
13.	Doing the dishes	0	1	2	3	4	5
14.	Sweeping/vacuuming	0	1	2	3	4	5
15.	Making the bed	0	1	2	3	4	5
16.	Shopping	0	1	2	3	4	5
17.	Doing laundry	0	1	2	3	4	5
18.	Washing the car	0	1	2	3	4	5
19.	Mowing the lawn	0	1	2	3	4	5
20.	Watering the lawn	0	1	2	3	4	5
21.	Sexual activities	0	1	2	3	4	5

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0	None at all
1	
2	
3	
4	Severe
5	Maximum or unable to do because of breathlessness

How much do the following limit you in your daily life?

22.	Shortness of breath	0	1	2	3	4	5
23.	Fear of "hurting myself" by overexertion	0	1	2	3	4	5
24.	Fear of shortness of breath	0	1	2	3	4	5

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Appendix 8
EuroQol 5-Dimension Questionnaire, 5-Level Version

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Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

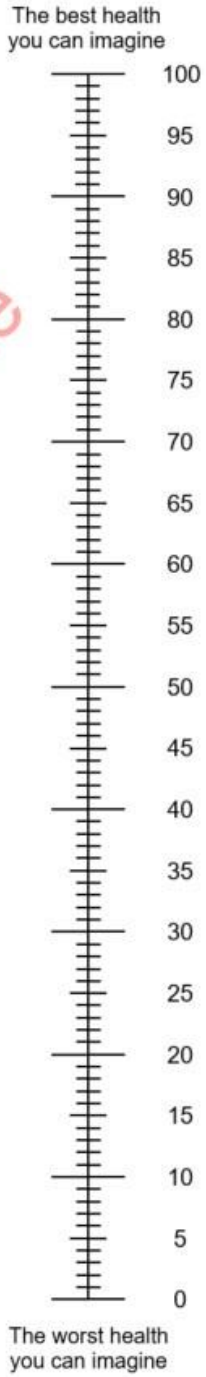
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 9
National Cancer Institute Common Terminology Criteria for Adverse Events

The United States of America (USA) National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE, v.5.0) can be found on the following website.

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

[Accessed: 21 September 2019]

This version of CTCAE is compatible at the AE (Adverse Event) term level where each CTCAE term is a Medical Dictionary for Regulatory Activities Terminology (MedDRA) LLT (Lowest Level Term). CTCAE v5.0 includes 811 AE terms and 26 'Other, specify' options for reporting text terms not listed in CTCAE. Each AE term is associated with a 5-point severity scale.

Appendix 10
Method of Eligibility Verification and Implementation of Randomization

Screening

Patients who are candidates for screening into the study will be evaluated for eligibility by the investigator to ensure that all eligibility criteria have been satisfied for randomization. The Screening period starts once Informed Consent is signed and ends at randomization.

Additional guidance on specific eligibility criteria follows.

- Inclusion Criterion: Idiopathic pulmonary fibrosis (IPF) diagnosis is made by the site, per the 2018 *IPF* Clinical Practice Guidelines by American Thoracic Society (ATS), the European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and the Latin American Thoracic Society (ALAT) (Raghu et al. 2018). For purposes of this trial patients with a clinical context suggestive of IPF and with high-resolution computed tomography (HRCT) pattern of usual interstitial pneumonia (UIP) or probable UIP are considered to have a diagnosis of IPF when biopsy is not available (Raghu et al. 2019).
- An HRCT of adequate quality, as determined by the central reviewer, obtained within 12 months prior to Screening is required for confirmation of eligibility. If an HRCT of adequate quality is not available within 12 months prior to Screening, an HRCT must be obtained during Screening for eligibility verification. All HRCT scans intended for eligibility verification will be sent for central radiology review. Please refer to the relevant study document for details on quality criteria and transmission of HRCT.
- The reference set for spirometry is *GLI2012 (Quanjer et al. 2012).*

HRCTs and biopsies, if available *should be sent for central review to* verify the pattern(s) is consistent with IPF diagnosis. If historical HRCTs are used for verification of diagnosis the guidelines in Table 1 should be followed. In addition, assessment of the extent of emphysema *will* be ascertained by central radiology review, to ensure eligibility criteria are met. *Patients with emphysema on ≥ 50% of the HRCT scan, or where* the emphysema is greater than the extent of fibrosis*, will not be eligible.*

Table 1 HRCT and Histopathology Criteria *to determine IPF diagnosis*

		No Biopsy	Histopathology Pattern			
			UIP	Probably UIP	Indeterminate for UIP	Alternative diagnosis
HRCT Pattern	UIP	Eligible	Eligible	Eligible	Eligible	NOT Eligible
	Probably UIP	Eligible	Eligible	Eligible	Eligible	NOT Eligible
	Indeterminate for UIP	NOT Eligible	Eligible	Eligible	NOT Eligible	NOT Eligible
	Alternative diagnosis	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible

UIP = usual interstitial pneumonia

REFERENCES

Quanjer PH, Stanojevic S, Cole TJ,; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012:40:1324–43.

Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Resp Crit Care Med 2018;198:e44–68.

Raghu G, Remy-Jardin M, Myers JL, et al. The 2018 Diagnosis of Idiopathic Pulmonary Fibrosis Guidelines: Surgical Lung Biopsy in Probable UIP is Not Mandatory. Am J Resp Crit Care Med 2019;200:1089–92.

Appendix 11
Borg Scale for Rating Dyspnea and Overall Fatigue (CR10)

0	Nothing at all	
0.3		
0.5	Extremely weak	Just noticeable
0.7		
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	Extremely strong	"Maximal"
11		
∿		
●	Absolute maximum	Highest possible

Borg CR10 Scale®
© Gunnar Borg, 1982, 1998, 2004
English

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Protocol - WA42293 - ZINPENTRAXIN ALFA - v5 - Published

Approval Task	[redacted] Company Signatory 28-Apr-2022 08:59:34 GMT+0000