Official Title: A Phase III Open-Label Extension Study to Evaluate Long-Term Safety and Efficacy of PRM-151 in Patients With Idiopathic Pulmonary Fibrosis (IPF)

NCT Number: NCT04594707

Document Dates: Protocol Version 4: 28-April-2022

PROTOCOL

TITLE:	**A PHASE III OPEN-LABEL EXTENSION STUDY TO EVALUATE LONG-TERM SAFETY AND EFFICACY OF PRM-151 IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF)**
PROTOCOL NUMBER:	WA42294
VERSION NUMBER:	4
EUDRACT NUMBER:	2020-001429-30
IND NUMBER:	110,774
NCT NUMBER:	NCT04594707
TEST PRODUCT:	Recombinant human pentraxin-2 (rhPTX-2; PRM-151) *[Zinpentraxin Alfa]*
MEDICAL MONITOR:	[redacted], MBBS
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**
4	See electronic date stamp on the final page.	—	—	—
3	1 February 2022	—	—	—
2	17 November 2020	—	—	—
1	10 July 2020	VHP	1	16 November 2020

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol WA42294 has been amended to incorporate changes made to include new information and identified risk of first and second generation PRM-151 drug product. Changes to the protocol, along with a rationale for each change, are summarized below.

- 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)

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

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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

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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 long-term safety, efficacy and pharmacokinetics of open-label PRM-151 in patients with idiopathic pulmonary fibrosis (IPF). Specific objectives and corresponding endpoints for the study are outlined below.

SAFETY OBJECTIVE

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

- Incidence and severity of all adverse events (AEs), with severity determined according to the 5-point severity scale (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI CTCAE, v.5.0])
- Incidence and severity of infusion related reactions (IRRs) and other AEs of special interest
- Proportion of patients permanently discontinuing study treatment due to AEs
- Change from baseline of targeted clinical laboratory test results

EFFICACY OBJECTIVES

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

- Annual rate of change in FVC (mL)
- Annual rate of change in 6-minute walk distance (6MWD)
- Annual rate of change in FVC% predicted
- Annual rate of change in DL_{CO}
- Time to disease progression, defined as time to first occurrence of ≥10% absolute decline in % predicted FVC, ≥15% relative decline in 6MWD, or death
- Survival, as measured by all-cause mortality
- IPF-related mortality and respiratory-related mortality

Exploratory Efficacy Objective

Exploratory analyses may also be performed for additional measures and subgroups of interest including concurrent use of IPF treatment and geographic region on the basis of the following endpoints:

- Change from baseline in University of California, San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ)
- Change from baseline in St. George Respiratory Questionnaire (SGRQ) Total Score
- 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
- Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF

Details of all such analyses will be provided in the Statistical Analysis Plan (SAP).

PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize pharmacokinetics of PRM-151 in patients with IPF (from Cohort A, and Cohort B, who are enrolled in the WA42293 study prior to 1 June 2022), on the basis of the following endpoint:

- 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 endpoints:

- 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 in patients with IPF (from Cohort A and Cohort B patients who enrolled into the WA42293 prior to 1 June 2022) 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 (from Cohort A and Cohort B) is to identify and/or evaluate biomarkers that can provide evidence of PRM-151 activity and the duration of that activity (i.e., pharmacodynamic biomarkers), are associated with acquired resistance to PRM-151, are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:

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

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 SOC on the basis of the following endpoint:

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

STUDY DESIGN

DESCRIPTION OF STUDY

This OLE study is being conducted to confirm the long-term safety, efficacy, and pharmacokinetics of PRM-151 in the treatment of eligible patients with IPF who have taken part in Study PRM-151-202 and received the open-label study drug (Cohort A) or completed the Phase III Study WA42293 (Cohort B) with PRM-151. Additionally, patients who have discontinued treatment from or have completed Study WA42293 and do not want to receive open-label PRM-151 in this study, will be invited to enroll in survival follow-up Cohort C. Patients in Cohort C will not receive any treatment and will not undergo any safety or efficacy assessments during the study. Patients who discontinue treatment from Cohorts A and B will automatically transition to Cohort C for long-term follow-up, unless they withdraw consent from the study.

Patients meeting the eligibility criteria for the study will receive PRM-151 10 mg/kg Q4W. Throughout the study, patients will be monitored for safety by collection of AEs (both serious and non-serious) and by regular physical exam and safety laboratory assessments.

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, or acute IPF exacerbations.

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

Dyspnea, fatigue, and blood oxygen saturation levels (SpO2) will be assessed based on measurements taken during the 6-minute walk test (6MWT). Chest HRCT will be assessed for changes from Study WA42293 to Week 52 (OLE) and Week 104 (OLE), for patients in Cohort B who had a HRCT scan at Screening and Week 52 in Study WA42293. Treated patients will be followed-up until the end of the study period, unless the patient withdraws consent for follow-up or death occurs.

For all patients receiving anti-fibrotic therapy, the investigator should document the dose, frequency, and duration of the anti-fibrotic drug.

During the study, patients may initiate pirfenidone or nintedanib, if determined to be clinically indicated by the investigator. The Study Investigator is required to document the specific reason for introducing anti-fibrotic therapy in patients who started the study not on anti-fibrotic therapy.

Approximately 600–700 patients are expected to enroll in the study. Patients will initially receive loading doses of either PRM-151 10 mg/kg IV infusion and/or placebo over 50–70 minutes on Days 1, 3, and 5, then one infusion of PRM-151 Q4W until the end of the study. Patients previously on the placebo arm of Study WA42293 will receive PRM-151 in all three loading doses, whereas patients previously on the active treatment arm of Study WA42293 will receive PRM-151 for the first dose, followed by placebo doses at the 2nd and 3rd loading dose visit. The loading doses will be blinded for Cohort B, to ensure that the blind in Study WA42293 is maintained for patients, site staff, and the Sponsor.

Patients entering Cohort A, from Study PRM-151-202 will have an eligibility visit prior to commencing dosing. The eligibility visit can occur on the same day as the dosing visit, if the patient is confirmed to be eligible for the study.

Patients entering Cohort B, from Study WA42293 will have their end-of-WA42293-study visit at Week 52. All assessments from the Week 52 WA42293 study visit must be completed prior to commencing dosing in the OLE study. Ideally, patients will be enrolled into Cohort B on the same day as their Week 52 (Study WA42293) visit.

Patients enrolling into Cohort C from Study WA42293 (e.g., those who do not wish to receive study treatment), or those who transition from Cohorts A and B, will be followed-up for the duration of this study, to collect their survival data.

NUMBER OF PATIENTS

Approximately 600-700 patients with IPF will be enrolled in this study.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- In the opinion of the Principle Investigator, participation in the study is in the best interest of the patient
- Ability to comply with the requirements of the study protocol, according to the investigator's best judgment
- Taken part in a previous study of PRM-151, as follows:
  - Participated in Study PRM-151-202 (completed the 28-week placebo-controlled period and entered the OLE), and tolerated the study drug in the opinion of the investigator (Cohort A) OR
  - Completed study treatment in Study WA42293 (Cohort B) OR
- Participated in Study WA42293 but discontinued from study treatment (Cohort C; patients who completed treatment in Study WA42293, but no longer wish to take PRM-151 may also join Cohort C).

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 8 weeks after the final dose of PRM-151.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 8 weeks after the final dose of PRM-151 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- Received any experimental treatment other than PRM-151 within 4 weeks or five half-lives of the experimental drug, whichever is longer, prior to the first dose in the OLE study
- Receiving strong inhibitor or inducer of CYP1A2 in patients taking pirfenidone
- Receiving potent inhibitor or inducer of P-gp in patients taking nintedanib
- Acute respiratory or systemic bacterial, viral, or fungal infection at the first visit of the OLE, or within 2 weeks of the first visit for patients joining Cohort A (from Study PRM-151-202)
- History of smoking (including cigarette, cannabis, cigar, pipe, and vaping) within 3 months prior to the first visit in the OLE
- History of alcohol or substance use disorder within 2 years prior to the first visit of OLE or known or suspected active alcohol or substance-use disorder
- History of severe allergic reaction or anaphylactic reaction to PRM-151
- Clinically significant abnormality on ECG during eligibility assessment that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Prolonged corrected QT interval >450 ms (for men) or >470 ms (for women) based on the Fridericia correction formula.
- Clinically significant laboratory test abnormalities (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient.
- Any of the following laboratory abnormalities known at the time of the first visit
  - ALT and/or AST $\geq 2.5\times$upper limit of normal (ULN)
  - Total bilirubin $\geq 2\times$ULN
- Pregnant or breastfeeding, or intending to become pregnant during the study (for Cohort A or B patients).

END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. The end of the study is expected to occur by 31-December-2028. This date may be subject to change, depending on the local commercial availability of PRM-151. Site discontinuation will occur upon commercial availability of PRM-151 in order for patients to transition off from this trial and onto commercially available PRM-151.

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 will receive IV infusions of 10 mg/kg PRM-151 over 50–70 minutes, with dose based on the patient's weight recorded at each visit (for loading or reloading doses, weight taken at the clinic visit for the first dose can be applied to the 2nd and 3rd doses).

Non-Investigational Medicinal Products

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

STATISTICAL METHODS

Because of the non-comparative character of the study, no statistical tests are planned. Demographic and baseline characteristics such as age, sex, race/ethnicity, concomitant IPF medication use, comorbid illnesses, and pulmonary function will be summarized by use of descriptive statistics.

Cohort B collected data will not be analyzed before unblinding of the code of the treatment received by the patient during the parent Study WA42293.

Additional safety update analyses may be conducted as required by Health Authorities. The final analysis will take place after the LPLV.

Patient efficacy data will be summarized by cohort including all patients who receive at least one dose of PRM-151 study drug. Efficacy in Cohorts A and B will be assessed by annual rate of change in FVC (mL), 6MWD, FVC% predicted, and DL_{CO}, time to disease progression, and survival as measured by all-cause mortality, IPF related mortality and respiratory related mortality. The annual rate of change in FVC (mL), 6MWD, FVC% predicted, and DL_{CO} will be calculated using the slope from a linear mixed effect model with random intercept (subject) and random slope (time), using measurements collected at each time point in this study.

Data from patients initially allocated to Cohort C will be used for survival follow-up only, without any safety or efficacy assessments. Further analysis details on all cohorts will be provided in the SAP.

DETERMINATION OF SAMPLE SIZE

The number of patients enrolled in the OLE study is approximately 600-700 (i.e., eligible patients from Study PRM-151-202 [Cohort A] and Study WA42293 [Cohorts B and C]). No formal sample size calculations were performed.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWD	6-minute walk distance
6MWT	6-minute walk test
ADA	anti-drug antibody
AE	adverse event
ALAT	Latin American Thoracic Society
ATS	American Thoracic Society
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DAMP	damage-associated molecular patterns
DL_{CO}	diffusing capacity for carbon monoxide
EC	Ethics Committee
ECM	extracellular matrix
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
ERS	European Respiratory Society
FAS	full analysis set
FcγR	Fc gamma receptors
FDA	Food and Drug Administration
FVC	forced vital capacity
HIPAA	Health Insurance Portability and Accountability Act
hPTX-2	human pentraxin-2
HRCT	high-resolution computed tomography
ICH	International Council for Harmonization
iDMC	independent Data Monitoring Committee
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INN	*International Nonproprietary Name*
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IxRS	interactive voice or web-based response system

Abbreviation	Definition
JRS	Japanese Respiratory Society
LB	lung biopsy
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NGS	next-generation sequencing
NIMP	noninvestigational- medicinal product
NMPA	National Medical Products Administration
OLE	open-label extension
PD	pharmacodynamics
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
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGRQ	St. George Respiratory Questionnaire
SOC	standard of care
SpO2	blood oxygen saturation levels
TEAE	treatment emergent adverse event
TEDE	Total Effective Dose Equivalent
UCSD-SOBQ	University of California, San Diego-Shortness of Breath Questionnaire
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 (LB). Historically, patients who received a diagnosis of IPF required a surgical LB; 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%-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 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 exacerbation 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 Fc gamma receptors (FcγR) 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 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 25,462.5 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.

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 intravenous (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 (PRM-151G-101). For more information on nonclinical or clinical investigations, 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 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 (α-Gal) at low levels in both 1st and 2nd generation PRM-151. The highest level of α-Gal observed was 0.3% in 1st generation batches. For 2nd generation PRM-151, levels <3% of α-Gal have been observed.

The Sponsor conducted an assessment of safety regarding the α-Gal glycan and concluded that PRM-151 containing α-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

Study WA42294 is a Phase III open-label extension (OLE) study to assess the long-term safety, efficacy, and pharmacokinetics of PRM-151 in patients with IPF with or without concurrent treatment with pirfenidone or nintedanib. Patients with IPF who have already completed the Phase II 28-week placebo-controlled period (PRM-151-202) and taken part in the OLE (Cohort A); or completed the Phase III Study WA42293 will be eligible to enroll in this study (Cohort B). Additionally, patients who have discontinued treatment or completed the Phase III Study WA42293, and do not wish to receive open-label PRM-151 in this study will be followed-up for survival (Cohort C). No safety or efficacy assessments will be required for these patients.

This open-label design will allow an examination of the impact of longer treatment duration on safety, durability of response in lung function, exercise tolerance, and patient reported outcomes as well as pharmacokinetics of PRM-151.

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 PRM-151-202, both for change in FVC (% predicted) and 6MWD through 28 weeks of treatment. Based on encouraging Phase I and II data in patients with IPF, PRM-151 has the potential to be a well-tolerated, disease modifying treatment for a broad spectrum of fibrotic diseases, including IPF.

In the Phase II study (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 (SAEs) reported during the study were considered related to the study treatment.
- Treatment-emergent adverse events (TEAE; serious and non-serious) leading to temporary discontinuation of study treatment were more common in the PRM-151 group than the placebo group overall (6 patients [7.8%] and 1 patient [2.6%], respectively), but these events were distributed across a range of body systems with no single preferred term reported in more than 1 patient and did not appear to indicate a safety risk for PRM-151.
- The most common adverse event (AE) assessed as possibly or probably related to study treatment was fatigue (16 events in 9 patients from the PRM-151 group [11.7%] and 3 events in 3 patients from the placebo group [7.7%]).
- Adverse events of cough with possible or probable relationship to study treatment were reported in 7 patients from the PRM-151 group (9.1%; seven events). No

patient from the placebo group was reported with possibly or probably related cough AEs.

- Four infusion-related reactions (IRRs) occurred in 3 patients: 2 patients in the PRM-151 group (2.6%), and 1 patient in the placebo group (2.6%). One patient in the PRM-151 group experienced dizziness and another experienced a hypertensive crisis event; 1 patient in the placebo group experienced 2 hypertensive crisis events. There was no difference between treatment arms in the nature or frequency of IRRs. None of the IRR events were deemed serious. There were no IRR events among the 7 patients with anti-drug antibodies (ADAs [6 patients in the PRM-151 group; 1 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, nor 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" 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 2500 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. Only patients enrolled in Cohort B, who had HRCT at screening and Week 52 in Study WA42293, will have further HRCT imaging at Week 52 and Week 104 during this extension study.

2. OBJECTIVES AND ENDPOINTS

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

2.1 SAFETY OBJECTIVE

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

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

2.2 EFFICACY OBJECTIVES

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

- Annual rate of change in FVC (mL)
- Annual rate of change in 6-minute walk distance (6MWD)

- Annual rate of change in FVC% predicted
- Annual rate of change in DL_{CO}
- Time to disease progression, defined as time to first occurrence of ≥10% absolute decline in % predicted FVC, ≥15% relative decline in 6MWD, or death
- Survival, as measured by all-cause mortality
- IPF-related mortality and respiratory-related mortality

2.3 EXPLORATORY EFFICACY OBJECTIVE

Exploratory analyses may also be performed for additional measures and subgroups of interest including concurrent use of IPF treatment and geographic region on the basis of the following endpoints:

- Change from baseline in University of California, San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ)
- Change from baseline in St. George Respiratory Questionnaire (SGRQ) Total Score
- 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
- Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF

Details of all such analyses will be provided in the Statistical Analysis Plan (SAP).

2.4 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is to characterize pharmacokinetics of PRM-151 in patients with IPF (from Cohort A, and Cohort B, who are enrolled in the WA42293 study prior to 1 June 2022), on the basis of the following endpoint:

- 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 endpoints:

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

2.5 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to PRM-151 in patients with IPF (from Cohort A and Cohort B patients who enrolled into the WA42293 prior to 1 June 2022) 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

2.6 BIOMARKER OBJECTIVE

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

- Relationship between biomarkers in blood listed in Section 4.5.10 and safety, efficacy, PK, immunogenicity, or other biomarker endpoints

2.7 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 SOC on the basis of the following endpoint:

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

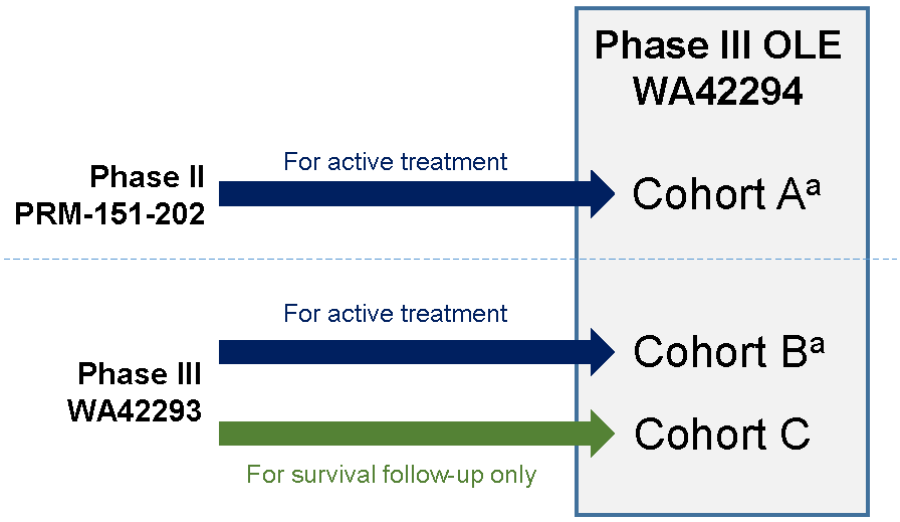
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overall Study Design and Plan

This OLE study is being conducted to confirm the long-term safety, efficacy, and pharmacokinetics of PRM-151 in the treatment of eligible patients with IPF who have taken part in Study PRM-151-202 and received the open-label study drug (Cohort A) or completed the Phase III Study WA42293 (Cohort B) with PRM-151. Additionally, patients who have discontinued treatment from or have completed Study WA42293 and do not want to receive open-label PRM-151 in this study, will be invited to enroll in survival follow-up Cohort C. Patients in Cohort C will not receive any treatment and will not undergo any safety or efficacy assessments during the study (see Figure 1 and Appendix 2). Patients who discontinue treatment from Cohorts A and B will automatically transition to Cohort C for long-term follow-up, unless they withdraw consent from the study.

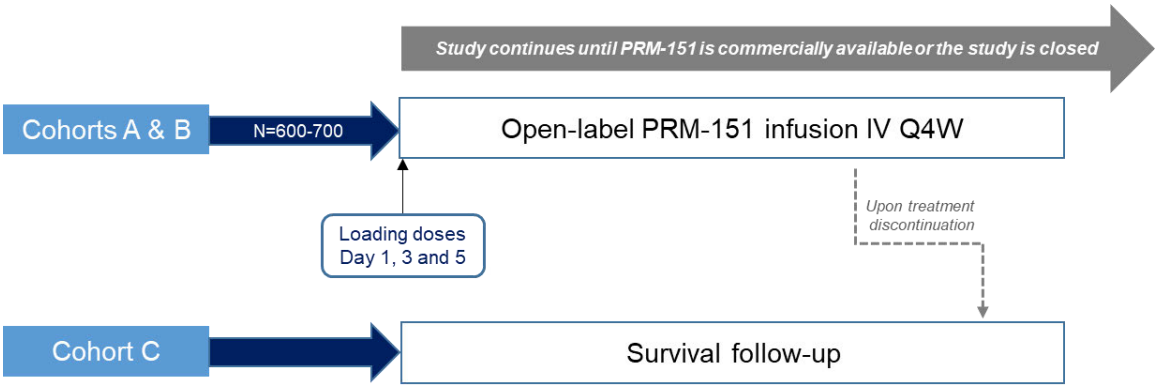
Figure 1 Cohort Allocation



[a] Only Cohorts A and B receive active treatment

Figure 2 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 2 Study Schema



IV=intravenous; Q4W=every 4 weeks.

Patients meeting the eligibility criteria for the study will receive PRM-151 10 mg/kg Q4W. Throughout the study, patients will be monitored for safety by collection of AEs (both serious and non-serious) and by regular physical exam and safety laboratory assessments.

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, or acute IPF exacerbations.

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

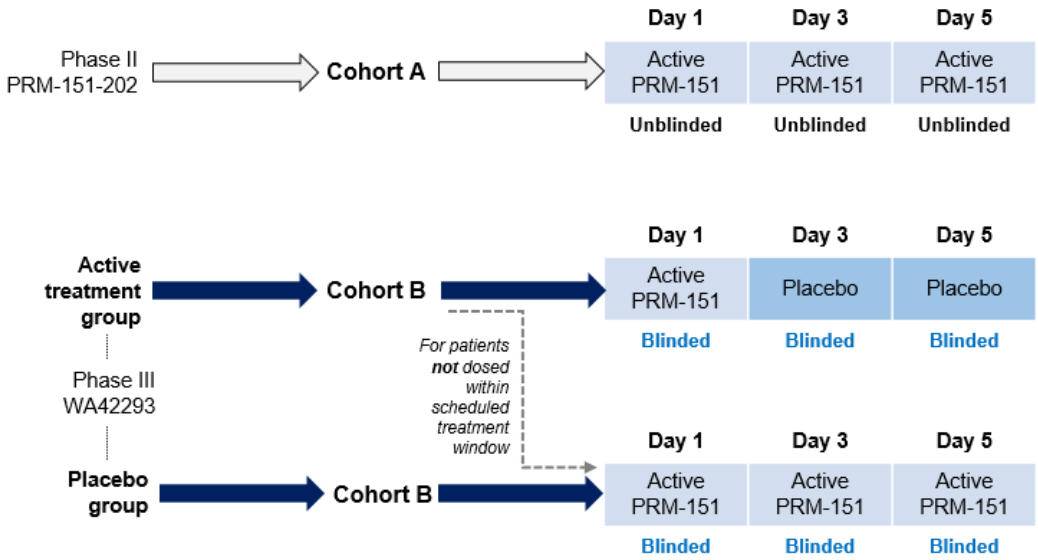
Dyspnea, fatigue, and blood oxygen saturation levels (SpO2) will be assessed based on measurements taken during the 6-minute walk test (6MWT). Chest HRCT will be assessed for changes from Study WA42293 to Week 52 (OLE) and Week 104 (OLE), for patients in Cohort B who had a HRCT scan at Screening and Week 52 in Study WA42293. Treated patients will be followed-up until the end of the study period, unless the patient withdraws consent for follow-up or death occurs.

For all patients receiving anti-fibrotic therapy, the investigator should document the dose, frequency, and duration of the anti-fibrotic drug.

During the study, patients may initiate pirfenidone or nintedanib, if determined to be clinically indicated by the investigator. The Study Investigator is required to document the specific reason for introducing anti-fibrotic therapy in patients who started the study not on anti-fibrotic therapy.

Approximately 600–700 patients are expected to enroll in the study. Patients will initially receive loading doses of either PRM-151 10 mg/kg IV infusion and/or placebo over 50–70 minutes on Days 1, 3, and 5, then one infusion of PRM-151 Q4W until the end of the study. Patients previously on the placebo arm of Study WA42293 will receive PRM-151 in all three loading doses, whereas patients previously on the active treatment arm of Study WA42293 will receive PRM-151 for the first dose, followed by placebo doses at the 2nd and 3rd loading dose visit. The loading doses will be blinded for Cohort B, to ensure that the blind in Study WA42293 is maintained for patients, site staff, and the Sponsor (see Figure 3).

Figure 3 Initial Loading Doses for Cohorts A and B



Patients entering Cohort A, from Study PRM-151-202 will have an eligibility visit prior to

commencing dosing. The eligibility visit can occur on the same day as the dosing visit, if the patient is confirmed to be eligible for the study.

Patients entering Cohort B, from Study WA42293 will have their end-of-WA42293-study visit at Week 52. All assessments from the Week 52 WA42293 study visit must be completed prior to commencing dosing in the OLE study. Ideally, patients will be enrolled into Cohort B on the same day as their Week 52 (Study WA42293) visit.

Patients enrolling into Cohort C from Study WA42293 (e.g., those who do not wish to receive study treatment), or those who transition from Cohorts A and B, will be followed-up for the duration of this study, to collect their survival data.

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. The end of the study is expected to occur by 31 December 2028. This date may be subject to change, depending on the local commercial availability of PRM-151. Site discontinuation will occur upon commercial availability of PRM-151 in order for patients to transition off from this trial and onto commercially available PRM-151.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for PRM-151 Dose and Schedule

Dose selection and dosing frequency in the PRM-151 trials are based on prior nonclinical and clinical data demonstrating favorable safety and efficacy at doses up to 10 mg/kg IV.

Most recent data from 111 patients enrolled in the 128-week open-label extension of Study PRM-151-202 have shown durability of effect of PRM-151 at 10 mg/kg Q4W up to 76 weeks in patients randomized to the active arm. Furthermore, patients in the placebo group crossing over to receive PRM-151 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.

The dose for this open-label extension study of PRM-151 is a continuation of the dose used in the previous Phase II and III trials of PRM-151 in IPF.

PRM-151 will be administered at 10 mg/kg on Days 1, 3, and 5 followed by Q4W administration thereafter.

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 nonclinical models to ensure that levels of PTX-2 would increase 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.

Phase-I, multiple-ascending dose, 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 Study PRM-151-202, and repeat loading doses were administered in the 128-week open-label extension (PRM-151-202) every 28 weeks.

Given the longer duration of this proposed study, it is expected that there may be occasional dose interruptions. Repeat loading of PRM-151 will be required on the resumption of study treatment at Days 1, 3, and 5 if any dose of study drug is missed (see Section 4.3.2). This is to ensure adequate tissue exposure of PRM-151, given the estimated tissue half-life of PTX-2 (24–30 days, see the PRM-151 Investigator's Brochure for further detail).

3.3.2 Rationale for the Study Design

Enrolling patients from both Study PRM-151-202 and pivotal Study WA42293 provides a larger sample size of patients treated with PRM-151, in order to assess long-term safety and efficacy of PRM-151, as well as survival data. This study will be open-label, as all patients enrolling into Cohorts A and B will receive active treatment with PRM-151. However, for Cohort B patients, the initial loading doses will be blinded, to maintain the integrity of the blind in the placebo-controlled study (Study WA42293). Following this, the remainder of the study treatments will be administered in an unblinded fashion, as will all treatments administered to patients in Cohort A.

FVC (mL) has been selected as a main efficacy outcome measure based on the common clinical use of this reproducible measure to monitor disease. Continuous assessment of FVC over a longer period of time will help determine the possible long-term effect of PRM-151 in the preservation of lung function in these patients.

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 (Collard et al. 2003; Saketkoo et al. 2014).

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 24–45 meters has been reported as clinically important in the IPF population (du Bois et al. 2011; Verma et al. 2011; Nathan et al. 2013). A change of 14–30.5 meters has been found to be clinically important across multiple patient groups (Bohannon and Crouch 2016), and the 6MWT 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 meters 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).

The data from Study PRM-151-202 (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 meters. A continuous assessment of this endpoint in the current long-term OLE study will help understand the effect of PRM-151 on exercise tolerance in patients with IPF.

3.3.3 Rationale for Collection of Survival Data in Cohort C

Patients with IPF have a very poor prognosis despite the availability of pirfendone and nintedanib. Median survival remains low, between 2–5 years (Jo et al. 2018). IPF is the primary cause of death for 60% of patients with IPF, with death commonly occurring after an acute exacerbation of the disease. When an acute exacerbation of IPF is not the cause of death, other common causes include acute coronary syndromes, congestive heart failure, lung cancer, infection, and venous thromboembolic disease (Frankel and Schwarz 2009).

For patients who are unable or unwilling to continue with study treatment and/or assessments, the Sponsor will continue to collect their survival data unless patients withdraw consent to do so.

3.3.4 Rationale for Biomarker Assessments

Exploratory biomarker samples will be collected from Cohort A and B during the study and may be used to assess PRM-151 pharmacodynamics and the relationship between IPF-related biomarkers, disease progression, and clinical status.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Approximately 600–700 patients with IPF will be enrolled in this study.

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- In the opinion of the Principle Investigator, participation in the study is in the best interest of the patient

- Ability to comply with the requirements of the study protocol, according to the investigator's best judgment
- Taken part in a previous study of PRM-151, as follows:
    - Participated in Study PRM-151-202 (completed the 28-week placebo-controlled period and entered the OLE), and tolerated the study drug in the opinion of the investigator (Cohort A) OR
    - Completed study treatment in Study WA42293 (Cohort B) OR
    - Participated in Study WA42293 but have discontinued from study treatment (Cohort C; patients who completed treatment in Study WA42293, but no longer wish to take PRM-151 may also join Cohort C)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 8 weeks after the final dose of PRM-151.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$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.

4.1.2 Exclusion Criteria

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

- Received any experimental treatment other than PRM-151 within 4 weeks or five half-lives of the experimental drug, whichever is longer, prior to the first dose in the OLE study.
- Receiving strong inhibitor or inducer of CYP1A2 in patients taking pirfenidone
- Receiving potent inhibitor or inducer of P-gp in patients taking nintedanib.
- Acute respiratory or systemic bacterial, viral, or fungal infection at the first visit of the OLE, or within 2 weeks of the first visit for patients joining Cohort A (from Study PRM-151-202).
- History of smoking (including cigarette, cannabis, cigar, pipe, and vaping) within 3 months prior to the first visit in the OLE.
- History of alcohol or substance use disorder within 2 years prior to the first visit of the OLE or known or suspected active alcohol or substance-use disorder.
- History of severe allergic reaction or anaphylactic reaction to PRM-151.
- Clinically significant abnormality on ECG during eligibility assessment that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Prolonged corrected QT interval >450 ms (for men) or >470 ms (for women) based on the Fridericia correction formula.
- Clinically significant laboratory test abnormalities (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient.
- Any of the following laboratory abnormalities known at the time of the first visit
  - ALT and/or AST $\geq 2.5 \times$ upper limit of normal (ULN)
  - Total bilirubin $\geq 2 \times$ ULN
- Pregnant or breastfeeding, or intending to become pregnant during the study (for Cohort A or B patients).

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

In this study all patients in Cohorts A and B will receive PRM-151.

Patients enrolling in Cohort A will receive three loading doses of open-label PRM-151 on Days 1, 3, and 5, followed by Q4W infusions.

For patients enrolling in Cohort B:

- Patients previously randomized to **placebo** in Study WA42293 will receive three loading doses on Days 1, 3, and 5 in a blinded fashion. All three doses will contain PRM-151.
- Patients previously randomized to **PRM-151** in Study WA42293 will receive three loading doses on Days 1, 3, and 5 in a blinded fashion. First of the three doses will contain PRM-151, whereas the subsequent two doses will contain placebo.
- In order to maintain the blind to the treatment assignment of Study WA42293, all patients in Cohort B will be dosed in a blinded fashion on Days 1, 3, and 5 of the initial loading dose (see Figure 3).

If the first loading dose in patients in Cohort B is delayed and occurs more than 3 weeks (21 days) after the Week 52 visit in Study WA42293, patients will receive all three loading doses with PRM-151 (in a blinded fashion).

To minimize bias in this study, patients and the evaluating physicians will be blinded to treatment assignment of Study WA42293 until all patients have either completed the study or discontinued early from the study, the Study WA42293 database is locked, and the Study WA42293 analyses are final.

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 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 will transition to second generation PRM-151 when made available in 2022.

4.3.1.2 Placebo for Initial Loading Dose

The 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.

On all dosing days, where applicable, dosing will occur after all efficacy and pre-dose safety assessments scheduled for that visit are completed. Patients will receive treatment on Study Days 1, 3, and 5, followed by infusions every 4 weeks (Q4W). If any scheduled Q4W infusions are missed, repeat loading doses will be required at the next scheduled visit (three doses, administered on alternate days).

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.

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

Medical personnel authorized by the investigator will be responsible for the administration of study drug and for observation of each patient throughout the study. Patients should be observed for at least 1 hour post infusion to monitor for IRRs. The 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. The dosing schedule includes the following:

- 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 administrations 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 should not be administered. This will be considered a "missed dose," and dosing should resume with 3 loading doses at the next scheduled visit.
- 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 (e.g., 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/pharmacodynamics (PD) samples may also be collected off-site.

4.3.3 Investigational Medicinal Product Handling and Accountability

PRM-151 and placebo required for completion of this study 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 interactive voice or webbased- response system (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

The sponsor will terminate the trial by 31 December 2028. This date may be subject to change, depending on the local commercial availability of PRM-151. Currently, the Sponsor does not have any plans to provide PRM-151 to patients who have completed the study. The Sponsor may evaluate whether to continue providing PRM-151 in accordance with 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 the day of 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 vaccines received will 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 (AE) 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 ≤10 mg daily) is permitted. Short-term, higher doses of corticosteroid may be required for acute medical emergencies (for example, 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 12–24 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 (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 safety or efficacy assessments, use of the following medications are prohibited during the study for patients in Cohorts A and B:

- 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, DL_{CO}, and 6MWT assessments
- Twice daily long-acting bronchodilators within 12 hours before pulmonary function testing, DL_{CO}, 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

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.

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.
- If not on nintedanib or pirfenidone treatment for IPF at study entry, patients may initiate (naive users) or re-start (prior users) nintedanib or pirfenidone, as rescue, if determined to be clinically indicated by the investigator 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.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is 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 Eligibility Assessments

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

All eligibility criteria should be confirmed before enrollment. Patients who are enrolling in the trial from Study PRM-151-202 should be assessed for eligibility against the study entrance criteria (Section 4.1). For these patients, screening assessments may be performed during an eligibility assessment visit prior to the first dosing visit in order to have time to get the laboratory results back from the central lab. Patients from Study WA42293 who enroll in the OLE study after a gap of 4 weeks or more should have their laboratory and safety assessments repeated prior to the first dose to confirm their eligibility.

4.5.2 Sequence of Assessments

On dosing days, dosing will occur after all safety and efficacy assessments scheduled for that visit are complete. When applicable, assessments should be completed as shown in Table 1. For loading or reloading doses, scheduled efficacy assessments will only be performed on the first of the three loading dose days, if applicable.

Table 1 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 – DL_{CO} 30–60 minute break – 6MWT
4	• HRCT (when completed on same day as other assessments) [a]
5	• Laboratory samples
6	• Study drug administration [b]

6MWT=6-minute walk test; DL_{CO} =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] In order to allow flexibility in scheduling, the HRCT can be performed at an earlier time on a different day.

[b] 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, providing 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.

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

The following data will be collected for patients who have enrolled in the study after a gap following the PRM-151 Study PRM-151-202. Data from Study WA42293 will be transferred to the OLE database that will include:

- Medical history: 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, including:
  - Pulmonary hypertension
  - Chronic obstructive pulmonary disease (COPD)/Emphysema

  - Lung cancer
  - Obstructive sleep apnea
  - Pulmonary embolism
  - Respiratory infections
  - 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, and hypercholesterolemia/hyperlipidemia,
  - Participation in supervised pulmonary or cardiac rehabilitation programs
  - Past surgical history
- Adverse events that are ongoing from Study WA42293.

All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from the day of initiation of study treatment will be recorded. For patients from Study PRM-151-202, medications used from 30 days prior to the initiation of study treatment will be recorded on the 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, nintedanib treatment; dose, duration of therapy, and reasons for discontinuation, if applicable). Additionally, history of all COVID-19 vaccinations received should be documented.

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

4.5.4 Physical Examinations

A complete physical examination should be performed for Cohort A patients at the eligibility assessment visit. This 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 for all patients at specified 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 at eligibility assessment visit for Cohort A. 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 saturation, 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 to be 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. Details on PFT procedures are available in the PFT manual. PFT data will be sent for central review.

DL_{CO} will be measured according to ATS/ERS guideline (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.

On visits at which spirometry and DL_{CO} are to be performed spirometry should be performed first, followed by DL_{CO}, and then 6MWT.

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

- Short-acting bronchodilator should not be used within 4 hours before pulmonary function, DL_{CO}, and 6MWT assessments.
- Once daily long-acting bronchodilators should not be used within 24 hours before pulmonary function testing, DL_{CO}, and 6MWT assessments.
- Twice daily long-acting bronchodilators should not be used within 12 hours before pulmonary function testing, DL_{CO}, 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 meters in length.

- An oxygen titration procedure will be performed for patients in cohort A 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 per local standard practice. Patients in Cohort B should maintain the same supplemental oxygen requirements as per study WA42293
- 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 O_2 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 PFTs, allowing for a short recovery period. 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 9) will be assessed just prior to and immediately following the completion of the 6MWT.

4.5.8 High-Resolution Computed Tomography

Patients in Cohort B who had high-resolution computed tomography (HRCT) at screening and Week 52 in Study WA42293, will have further HRCT imaging at Week 52 and Week 104 during this extension study.

Patients in Cohort A and C, and patients in Cohort B who did not have any HRCT scans in Study WA42293, will not be required to have any imaging during this study.

4.5.9 Assessment of Acute Exacerbations of IPF, Hospitalizations for Respiratory Causes, and Deaths (Adjudication 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 (applicable for Cohorts A and B only). 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.

4.5.9.1 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 AE of special interest (see Section 5.3.3) (or SAE as applicable).

All relevant AE 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 Adjudication Committee describes the process for the data to be reviewed and criteria for defining an IPF exacerbation.

4.5.9.2 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.

4.5.9.3 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 that occur in Cohort A or B 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. Deaths occurring in Cohort C will not be adjudicated.

4.5.9.4 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

4.5.10 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: chloride, potassium, BUN, creatinine, albumin, AST, total bilirubin, sodium, bicarbonate (CO2), calcium, glucose, ALK, ALT, total protein, C-reactive protein, estimated glomerular filtration rate.
- Coagulation tests: PT, PTT, INR
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at eligibility assessment visit. 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)

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 analysis

  Blood samples for determination of PRM-151 concentration will be collected from all IPF patients enrolled in Cohort A (see Appendix 3) and Cohort B patients who enrolled into the WA42293 prior to 1 June 2022 (see Appendix 4) for PK measurements
- Plasma concentration (including but not limited to predose PK samples) to measure the endogenous level of human pentraxin-2 [hPTX-2] will be analyzed from IPF patients enrolled in Cohort A and Cohort B patients who enrolled into the WA42293 prior to 1 June 2022.
- Serum and plasma samples for biomarker analysis will be collected from all IPF patients enrolled in both Cohort A (see Appendix 3) and Cohort B (see Appendix 4) for PD measurements.
- Blood PAXgene for RNA biomarker analysis will be collected from all patients with IPF enrolled in both Cohort A (see Appendix 3) and Cohort B (see Appendix 4) for PD measurements.

Circulating blood biomarkers that may provide information on PRM-151 pharmacodynamic activity or the course of fibrosis will be measured. 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 biomarker changes over time. If novel PTX-2 or IPF-related biomarkers are identified, they may be measured from stored blood, serum, or plasma.

Eligibility blood samples, from patients in Study PRM-151-202 Cohort A 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 4.5.13), 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 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 Roche Biosample Repository (see Section 4.5.13). 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 will be subject to the confidentiality standards described in Section 8.4.

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.

4.5.11 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.

4.5.12 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).

4.5.12.1 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.

4.5.12.2 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.

4.5.13 Optional Samples for Research Biosample Repository

4.5.13.1 Overview of the Research Biosample Repository

The Research Biosample Repository (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

4.5.13.2 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 4.5.13) will not be applicable at that site.

4.5.13.3 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:

- Urine samples collected as per Appendix 4.
- Leftover blood, serum, plasma and urine samples and any derivatives thereof (e.g., RNA, proteins, peptides)

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).

4.5.13.4 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.

4.5.13.5 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.

4.5.13.6 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.

4.5.13.7 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

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 (the first occurrence of the Grade 3 IRR can be either in the Phase II Study PRM-151-202, Phase III Study WA42293, or in this Study WA42294)
- 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, 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

safety data at time of the treatment discontinuation visit. Survival data will continue to be collected unless the patient declines to be included in Cohort C.

4.6.2 Patient Discontinuation from the Study

Patients will return to the clinic for a treatment discontinuation visit (4 weeks after the final dose), followed by a study discontinuation visit (4 weeks after the treatment discontinuation visit).

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.

For patients who withdraw from the study, survival status may be ascertained through the use of Death Registries, where approved and available, unless patients withdraw consent for such data collection.

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 Harmonization (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)
- Commercial availability of PRM-151

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. 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 AEs, 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 AEs 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.* Please 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

Infusion-related reaction 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 treatments 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 Study PRM-151-202 (n=116), 2 patients treated with PRM-151 (2.6%) experienced IRRs during the randomized period (in Weeks 1 and 8), and 10 patients treated with PRM-151 (9.0%) during the OLE period (occurring from Study 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 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 SAEs if appropriate (see Section 5.5). Health care professionals should also instruct patients on how to recognize the symptoms of any anaphylactic, or hypersensitivity reaction 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 continuing 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 SOC 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. 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, and Anaphylactic and Hypersensitivity Reactions

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

Table 2 Actions if an Infusion-Related Reactions (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 [c], 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 [c], 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: [b] • Permanently discontinue study drug treatment.
IRR (Grade 2 and Grade 3 [1 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 [1 occurrence]) resolved after continued treatment	• Restart study drug infusion at reduced rate (120 minutes). • Next study drug infusion should be at reduced rate and pre-medication should be used. [a] • 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] Diphenhydramine or clemastine and dexamethasone are recommended (see details in text below).

[b] The first occurrence of the Grade 3 IRR can be either in the Phase II Study PRM-151-202, Phase III Study WA42293, or in this Study WA42294.

[c] Serum tryptase should be collected between 1 and 6 hours after the event

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)
- Dexamethasone 10 mg IV (or an equivalent dose of a long acting corticosteroid)

If subsequent infusion(s) are uneventful, the investigator may resume 50–70 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 5.1.1.

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 a 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 an 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 PRM-151.

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.

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 study treatment 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 AEs, including SAEs 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 ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE 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
- AEs 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)

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- This does not include any AE 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 AE 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 AE (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 IRR with NCI CTCAE Grade ≥2
- Suspected anaphylactic and hypersensitivity reactions (all grades)
- Acute or suspected exacerbation of IPF (all grades)

5.3.4 Collection of Survival Data (Cohort C)

All efforts will be made to collect survival data for patients in Cohort C. Survival data collection will be accomplished remotely (i.e., via telephone or electronically), provided these communications are well documented.

Information on survival may be collected in multiple ways, including telephone calls or patient medical records, approximately every 6 months until death, or study termination by the Sponsor.

Women who become pregnant during the WA42293 study or in Cohort A or B of the WA42294 study can join Cohort C of WA42294 study.

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

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 AE 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 AEs, 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 SAEs 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). For patients in Cohort A and B, 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. Adverse events that are ongoing from study WA42293 for Cohort B patients will be transferred over from the WA42293 database in in the WA42294 Adverse Event eCRF.

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

Instructions for reporting AEs 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 3 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 3 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×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 AE.

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 AE 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 prior the first dosing 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 AE or a SAE:

- 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 SAE, but should be reported as an AE 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 AEs, but may result in AEs. Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated AE 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-151, AEs 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, regardless of whether they result in an AE, 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:

- SAEs (defined in Section 5.3.2; see Section 5.5.2 for details on reporting requirements)
- AEs 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 SAEs and AEs 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, SAEs and AEs 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. 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 SAE (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 SAE, 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 AE 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 SAEs 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.

5.6.2 All pregnancies reported during the study should be followed until pregnancy outcome. Sponsor Follow-Up

For SAEs, AEs 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), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, 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:

- 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 independent Data Monitoring Committee (iDMC) will be established to review safety data from this study only up until the time the database for primary analysis for Study WA42293 is locked, and Study WA42293 is unblinded to the Sponsor (i.e., for the duration of Study WA42293), thereby better ensuring the safety of study participants. Consistent with U.S. 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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All analyses will be reported separated by cohort. Not all analyses are applicable to all cohorts.

The safety analyses will be performed on the safety evaluable population, unless otherwise specified. Safety will be assessed through descriptive summaries of exposure to PRM-151 study drug, AEs, and laboratory test results.

All efficacy analyses will be performed on the full analysis set (FAS) population, unless otherwise specified. Participants in Cohort B will be analyzed by treatment as assigned at randomization in the parent study and for all patients overall.

Because of the non-comparative character of the study, no statistical tests are planned. Demographic and baseline characteristics such as age, sex, race/ethnicity, concomitant IPF medication use, comorbid illnesses, and pulmonary function will be summarized by use of descriptive statistics.

Cohort B collected data will not be analyzed before unblinding of the code of the treatment received by the patient during the parent Study WA42293.

Additional safety update analyses may be conducted as required by Health Authorities. The final analysis will take place after the LPLV.

The following sections are applicable to Cohorts A and B of the study. Data from patients initially allocated to Cohort C will be used for survival follow-up only, without any safety or efficacy assessments. Further analysis details on all cohorts will be provided in the SAP.

6.1 DETERMINATION OF SAMPLE SIZE

The number of patients enrolled in the OLE study is approximately 600–700 (i.e., eligible patients from Study PRM-151-202 [Cohort A] and Study WA42293 [Cohorts B and C]). No formal sample size calculations were performed.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal 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.

6.3 SAFETY ANALYSES

The safety analyses will include all patients who receive at least one administration (full or partial dose) of PRM-151 study drug.

Safety will be assessed through descriptive summaries of exposure to PRM-151 study drug, adverse events, SAEs, AESIs, and laboratory test results. Data will be reported by cohort.

6.3.1 Adverse Events

Verbatim descriptions of TEAE will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) and adverse event severity will be graded according to NCI CTCAE v5.0 scale. A TEAE is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug.

The incidence and observation time-adjusted rate will be summarized, as appropriate. In addition, separate summaries will be generated for serious adverse events, deaths, adverse events of special interest, and adverse events leading to discontinuation of PRM-151. Adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade.

6.3.2 Laboratory Data

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.

6.4 EFFICACY ANALYSES

Patient efficacy data will be summarized by cohort including all patients who receive at least one administration (full or partial dose) of PRM-151 study drug. Efficacy will be assessed by annual rate of change in FVC (mL), 6MWD, FVC% predicted, and DL_{CO}, time to disease progression , and survival as measured by all-cause mortality, IPF-related mortality and respiratory-related mortality. The annual rate of change in FVC

(mL), 6MWD, FVC% predicted, and DL_{CO} will be calculated using the slope from a linear mixed effect model with random intercept (subject) and random slope (time), using measurements collected at each time point in this study. Additionally, change from baseline to Weeks 52 and 104 in quantitative imaging analysis parameters of HRCT scan of the thorax will be summarized. All efficacy parameters will be summarized descriptively, and as all patients will be receiving PRM-151, there will be no hypothesis testing between treatment groups.

As is planned for the WA42293 study, in the assessment of spirometry data (FVC [mL], FVC% predicted, and DL_{CO}), all measurements that meet the minimal level of quality will be used. With respect to handling of missing data, for the purpose of determining the annual rate of change estimates, appropriate strategy will be adopted in this study for the data impacted by intercurrent events. For lung transplantation, a hypothetical strategy will be utilized where measurements collected after transplantation will not be used in the analysis, and values will be implicitly imputed from the model. For death, a composite strategy will be utilized where assessments following death will be assigned with values to designate treatment failure. Further details will be specified in the Statistical Analysis Plan. In addition, summaries using all observed data will be performed.

Kaplan-Meier estimates for the median and quartiles will be computed for time to disease progression (defined as time to first occurrence of $\geq$ 10% absolute decline in % predicted FVC, $\geq$ 15% relative decline in 6MWD, or death) and time to death; estimates will be presented together with their 95% confidence intervals.

6.5 EXPLORATORY EFFICACY ANALYSIS

Exploratory analyses will be performed on the following endpoints and may also be performed for additional endpoints and subgroups of interest including concurrent use of IPF treatment and geographic region:

- Change from baseline in University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ)
- Change from baseline in St. George Respiratory Questionnaire (SGRQ) Total Score
- 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
- Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF

All efficacy exploratory parameters will be summarized descriptively. For time to event endpoints, Kaplan-Meier estimates for the median and quartiles will be computed and estimates will be presented together with their 95% confidence intervals.

Further details for the exploratory analyses will be provided in the Statistical Analysis Plan.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to determine plasma 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 plasma 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.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment.

The number and percentage of ADA positive patients at baseline and during the study will be tabulated by cohort. The relationship between ADA status and safety, efficacy, and PK, may be analyzed and reported via descriptive statistics.

6.8 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.

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

6.9 HEALTH STATUS UTILITY ANALYSES

Annual rate of change in EQ-5D-5L health utility index-based and VAS scores will be summarized descriptively.

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, DL_{CO} 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 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/ or delegate CRO 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.

Upon treatment discontinuation, patients in Cohort A or B will automatically transition into Cohort C. Subjects who have discontinued treatment from or have completed study WA42293 and do not wish to receive open label PRM-151, and want to participate in the study, will be required to sign a Cohort C informed consent form.

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 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 600–700 patients. An IxRS will be used for study drug inventory management and to enroll patients onto 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 antibody 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 will be read centrally and managed by a central reading vendor(s).

An iDMC will be employed to monitor and evaluate patient safety in Study WA42294 only up until the time the database for primary analysis for Study WA42293 is locked, and Study WA42293 is unblinded to the Sponsor (i.e., for the duration of Study WA42293).

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 (for patients in Cohorts A and B only). 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).

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Appendix 1 Schedule of Activities for Cohorts A and B

Assessment	Eligibility assessment visit [a]	Baseline / Dosing Day 1 [b, c]	Dosing Day 3	Dosing Day 5	Week 4, then every 4 weeks	Week 12, then every 12 weeks	Week 24, then every 24 weeks	Treatment Discontinuation [d]	Study Completion/ Discontinuation [d]
Window	**4 weeks**	**Loading within 8 days [e]**			**(±5 days)**	**(±5 days)**	**(±7 days)**		
Visit number	**1**	**2**	**3**	**4**					
Informed Consent	x								
Demographics	x								
Medical History	x								
Inclusion/Exclusion	x								
Height (cm)	x								
Pregnancy Test (serum pregnancy analyzed at central lab) – WOCB only	x								
SAFETY ASSESSMENTS									
Vital Signs [f]	x	x	X	x	x				
Physical Exam [g]	x	x			x				
Weight (kg)	x	x			x				
AE/SAE Assessment		x	X	x	x			x	x
Prior/Concomitant Medications and Oxygen Use	x	x	X	x	x			x	x
ECG	x						x		

Appendix 1 Schedule of Activities for Cohorts A and B (cont.)

Assessment	Eligibility assessment visit [a]	Baseline /Dosing Day 1 [b, c]	Dosing Day 3	Dosing Day 5	Week 4, then every 4 weeks	Week 12, then every 12 weeks	Week 24, then every 24 weeks	Treatment Discontinuation [d]	Study Completion/ Discontinuation [d]
Window	**4 weeks**	**Loading within 8 days [e]**			**(±5 days)**	**(±5 days)**	**(±7 days)**		
Visit number	**1**	**2**	**3**	**4**					
LABORATORY ASSESSMENTS									
Blood Tests (Hematology, Chemistry, Coagulation) [h]	x	x			x	x		x	x
SARS-CoV-2 serology [i]		x				x			
Urine Pregnancy test (WOCB only)	x	x	X	x	x			x	x
Urinalysis		x				x			
Serum Tryptase, Complement C3, PK, ADA sample for ≥ Grade 2 Infusion-related reactions or suspected anaphylaxis or hypersensitivity reactions [j]		x							
PK, PD, and ADA Sampling		See Appendix 3 and Appendix 4							
EFFICACY ASSESSMENTS									
Healthcare utilization for respiratory events		x	X	x	x			x	x

Appendix 1 Schedule of Activities for Cohorts A and B (cont.)

Assessment	Eligibility assessment visit [a]	Baseline /Dosing Day 1 [b, c]	Dosing Day 3	Dosing Day 5	Week 4, then every 4 weeks	Week 12, then every 12 weeks	Week 24, then every 24 weeks	Treatment Discontinuation [d]	Study Completion/ Discontinuation [d]
Window	**4 weeks**	**Loading within 8 days [e]**			**(±5 days)**	**(±5 days)**	**(±7 days)**		
Visit number	**1**	**2**	**3**	**4**					
Assessment of IPF exacerbations and hospitalizations		x	x	x	x			x	x
Spirometry		x				x		x	
6-minute walk test and Borg Scale		x				x		x	
DL_{CO}		x					x	x	
Patient Reported Outcomes; SGRQ, UCSD-SOBQ and EQ-5D-5L [k]		x					x	x	
HRCT [l]		Weeks 52 and 104 for eligible patients in Cohort B [l]							
TREATMENT ASSESSMENTS									
Study drug dosing [m]		x	x	x	x				
Adherence to pirfenidone or nintedanib	x	x	x	x	x			x	x
Lung Transplantation Assessment		x							

Appendix 1 Schedule of Activities for Cohorts A and B (cont.)

ADA=anti-drug antibody; AE=adverse event; Discon.=discontinued; DL_{CO}=diffusing capacity for carbon monoxide; EOS=end of study; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; HRCT=high-resolution computed tomography; IPF=idiopathic pulmonary fibrosis; IRR=infusion-related reaction; 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; UCSD-SOBQ=University of California, San Diego–Shortness of Breath Questionniare; W52=Week 52; WOCB=women of childbearing potential.

[a] Eligibility visit can occur on the same day as dosing as long as eligibility criteria have been confirmed prior to dosing.

[b] Patients who are rolling-over from Study WA42293 will not be required to repeat safety and efficacy assessment at Day 1 if the visit occurs within 4 weeks of Week 52.

[c] Patients from the active treatment arm in Study WA42293 will be given placebo doses at Day 3 and Day 5.

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

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

[g] Full physical exam at eligibility visit and an abbreviated physical exam, thereafter.

[h] Clinical laboratories will be assessed every 4 weeks for the first 12 weeks and every 12 weeks thereafter.

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

[j] Blood samples for ADA, serum tryptase, and complement C3 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. Blood samples for ADA, serum tryptase, and complement C3 analyses should be obtained at the first follow-up visit after the events of suspected anaphylaxis, or hypersensitivity reactions.

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

[l] HRCT will be performed at Week 52 and Week 104 only for patients who had HRCTs performed during Study WA42293.

[m] Repeat loading doses will be required if patients miss any 4-weekly 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, if applicable. 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, providing 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.

Appendix 2 Schedule of Activities for Cohort C

Assessment	Survival follow-up
Window	**Every 6 months (±14 days)**
Survival Status [a]	x

[a] Following the last dose of study treatment, discontinuation of treatment, or if patient becomes pregnant, patients will enter the survival follow-up phase. Information on survival will be collected remotely every 6 months.

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Cohort A

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

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Cohort A

Visit	Timepoint	Window	Sample Type [a]
Week 12	Prior to the start of IV infusion	−2 to 0 hours	PRM-151 PK [b]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)
			PRM-151 ADA [b]
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [b]
			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 [b]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)
			PRM-151 ADA [b]
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [b]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)
Unscheduled visit [c]	NA	NA	PRM-151 PK [b]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)
			PRM-151 ADA [b]

ADA=anti-drug antibody; IPF=idiopathic pulmonary fibrosis; IV=intravenous; PD=pharmacodynamic; PK=pharmacokinetic.

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

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

[c] Up to 24 weeks of treatment, 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 biomarker samples should be taken prior to the start of the first loading dose.

Appendix 4 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Cohort B

Visit	Timepoint	Window	Sample Type [a]	Optional Biomarker Sample
Day 1	Prior to the start of IV infusion	−2 to 0 hours	PRM-151 PK [b]	Urine [d]
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	
			PRM-151 ADA [b]	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [b]	
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	
Day 3	Prior to the start of IV infusion	−2 to 0 hours	PRM-151 PK [b]	
			PRM151 PD biomarker (serum, plasma, and Paxgene- for RNA)	
Day 5	Prior to the start of IV infusion	−2 to 0 hours	PRM-151 PK [b]	
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [b]	
			PRM151 PD biomarker (serum, plasma, and Paxgene- for RNA)	
Weeks 4	Prior to the start of IV infusion	−2 to 0 hours	PRM-151 PK [b]	
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	
			PRM-151 ADA [b]	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [b]	
			PRM151 PD -biomarker (serum,plasma, and Paxgene for RNA)	
Weeks 12	Prior to the start of IV infusion	−2 to 0 hours	PRM-151 PK [b]	Urine [d]
			PRM151 PD biomarker (serum, plasma, and Paxgene- for RNA)	
			PRM-151 ADA [b]	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [b]	
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	

Visit	Timepoint	Window	Sample Type [a]	Optional Biomarker Sample

Appendix 4 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Cohort B

Week 24	Prior to the start of IV infusion	−2 to 0 hours	PRM-151 PK [b]	Urine [d]
			PRM151 PD biomarker (serum, plasma, and Paxgene- for RNA)	
			PRM-151 ADA [b]	
	2 hours after the start of IV infusion	±15 min	PRM-151 PK [b]	
			PRM151 PD biomarker (serum, plasma, and Paxgene for RNA)	
Unscheduled visit [c]	NA	NA	PRM-151 PK [b]	
			PRM-151 PD biomarker (serum, plasma, and Paxgene for RNA)	
			PRM-151 ADA [b]	
Every 12 weeks up to 2 years	Prior to the start of IV infusion	−2 to 0 hours		Urine [d]

ADA=anti-drug antibody; IPF=idiopathic pulmonary fibrosis; IV=intravenous; PD=pharmacodynamic; PK=pharmacokinetic.

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

b PK samples will be collected as plasma, and ADA samples will be collected as serum. PK/ADA samples will ONLY be collected from patients who enrolled into the WA42293 prior to 1 June 2022.

c Up to 24 weeks of treatment, 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 biomarker samples should be taken prior to the start of the first loading dose.

d The urine samples are optional and should be obtained from any individual from cohort B who signs the separate RBR Informed Consent Form to collect residual samples at assigned clinical visits, and only for up to 2 years.

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

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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…

Appendix 6: St. George's Respiratory Questionnaire

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 ☐

Appendix 6: St. George's Respiratory Questionnaire

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	☐	☐

Appendix 6: St. George's Respiratory Questionnaire

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

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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.

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

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

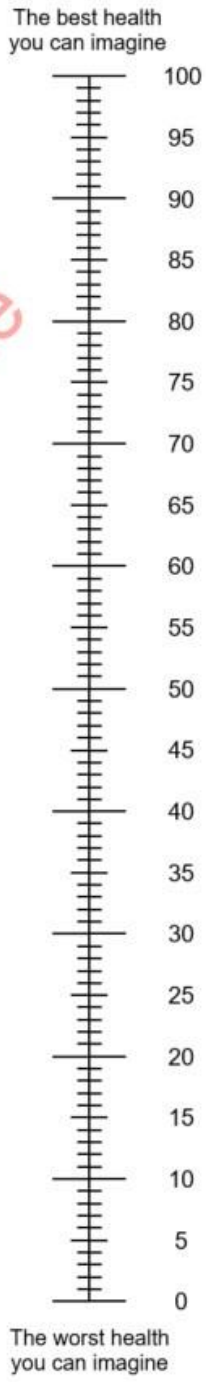
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

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 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

Signature Page for: System identifier:RIM-CLIN-438682
Protocol - WA42294 - ZINPENTRAXIN ALFA - v4 - Global/Core- Published

Approval Task	[redacted] Company Signatory 28-Apr-2022 09:00:20 GMT+0000