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Clinical Trial Protocol: Study PRM-151-202

Study Title:	A Pilot Trial to Evaluate the Efficacy of PRM-151 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Study Number:	PRM-151-202
Study Phase:	2
Product Name:	PRM-151
IND Number:	110,774
EUDRACT Number:	2014-004782-24
Indication:	Idiopathic Pulmonary Fibrosis (IPF)

Sponsor: Promedior, Inc
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	11 November 2014
Original Protocol:	Version 1.0

SYNOPSIS

Sponsor:
Promedior, Inc

Name of Finished Product:
Recombinant human Pentraxin-2; PRM-151

Study Title:
A Pilot Trial to Evaluate the Efficacy of PRM-151 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Study Number:
PRM-151-202

Study Phase: Phase 2

Investigational Product; Dose; and Mode of Administration:
PRM-151 10 mg/kg every 4 weeks via intravenous infusion over 60 minutes.
On all dosing days, dosing will occur ***after*** all safety and efficacy assessments scheduled for that visit are completed.

Comparator Dose; and Mode of Administration:
Placebo will be administered via IV infusion over 60 minutes.

Primary Objective:

- Demonstrate the superiority of PRM-151 to placebo in preservation or increase from baseline to 28 weeks in mean FVC% predicted in subjects on a stable dose of pirfenidone and subjects not on other treatment for IPF.

Secondary Objective(s):

- Demonstrate the superiority of PRM-151 to placebo in preservation or increase from baseline to 28 weeks in normal lung as quantified by structural imaging in subjects on a stable dose of pirfenidone and subjects not on other treatment for IPF.
- Assess the tolerability and safety of PRM-151 in subjects with IPF treated through 24 weeks
- Assess the ability of PRM-151 to reduce disease-related events associated with mortality
- Assess the ability of PRM-151 to preserve or increase 6 minute walk distance

Exploratory Objective(s):

- Assess the ability of PRM-151 to preserve or increase gas exchange
- Assess the impact of PRM-151 on disease related symptoms
- Assess the impact of PRM-151 on functional respiratory imaging parameters
- Assess the impact of PRM-151, disease pathogenesis and disease progression on exploratory serum, cellular and genetic biomarkers

Study Endpoints:

Primary:

- The primary endpoint is the mean absolute change from baseline in FVC % predicted from baseline to week 28.

Secondary:

1. **Structural Imaging:**
    - Mean absolute change from baseline at 28 weeks in total lung volume and volume of parenchymal features (normal, ground glass density, reticular changes, honeycombing, and low attenuation areas) using quantitative imaging software to measure absolute volume (in ml) and relative % of total lung volume.
    - Transitions between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and low attenuation areas) by quantitative imaging software.
2. **Safety**: Tolerability/safety will be assessed over the 24 week dosing period by the following parameters:
    - Incidence of AEs.
    - Incidence of serious adverse events (SAEs).
    - Incidence of respiratory AEs and SAEs.
    - Proportion of subjects discontinuing study drug due to AEs.
    - Change from Baseline in hematology and serum chemistries.
    - All-cause mortality.
    - Mortality due to respiratory deterioration.
3. **Disease related events associated with mortality**: The number of "respiratory decline" events over the 24 week dosing period as defined below:
    - Unscheduled visits to a healthcare professional for respiratory status deterioration.
    - Urgent care visit for respiratory status deterioration.
    - Hospitalization due to a worsening or exacerbation of respiratory symptoms.

    All "respiratory decline" events will be further characterized according to the definitions of IPF-related disease exacerbation, as defined according to American Thoracic Society (ATS) criteria (Raghu, Collard et al. 2011):
    - Unexplained worsening of dyspnea over 1 month.
    - Worsened or severely impaired gas exchange.
    - New radiographic alveolar infiltrates.
    - The absence of another reason for the worsening respiratory symptoms, (pulmonary embolism, congestive heart failure, pneumothorax).
    - Acute, unexplained decline in oxygen saturation over 1 month.
4. **Pulmonary Function Tests**
    - Time-weighted average (TWA) of change in FVC% predicted from Baseline to Week 28.
    - TWA of change in FVC in ml from Baseline to Week 28.
    - Proportion (%) of subjects with an absolute decline in FVC% predicted of ≥5% and ≥10% from Baseline to Week 28.

- Proportion (%) of subjects with an absolute decline in FVC of ≥ 100ml and ≥ 200ml from Baseline to Week 28.
- Proportion of subjects with an absolute increase in FVC % predicted of ≥5% and ≥10% from Baseline to Week 28.
- Proportion of subjects with an absolute increase in FVC in ml of ≥100ml and ≥ 200ml from Baseline to Week 28.
- Mean absolute change from baseline in % predicted diffusion capacity of carbon monoxide (DL_{CO}).
- Change in 6-minute walk distance, in meters, from baseline to Week 28.

Exploratory:

1. **Patient Reported Outcomes**
   - Change in Patient Reported Outcomes as measured by King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and Leicester Cough Questionnaire (LCQ) from baseline to Week 28.

2. **Quantitative Functional Respiratory Imaging**
   - Change from baseline to28 weeks in regional lung volumes, specific airway volumes and resistance as measured by quantitative imaging software (FluidDA).

3. **Biomarkers**
   - Changes in serum and cellular biomarkers and response according to baseline genetic characteristics: including but not limited toTLR3 L412F polymorphism, MUC5B promoter polymorphism.

Study Design:

This study is a Phase 2, randomized, double-blind, placebo controlled, pilot study designed to evaluate the efficacy and safety of PRM-151 administered through Week 24 to subjects with IPF. Subjects meeting the eligibility criteria for the study will be randomized to PRM-151 10 mg/kg every 4 weeks or placebo. Efficacy will be evaluated through pulmonary function tests (PFTs) including spirometry, Diffusion Capacity (DLco) and Total Lung Capacity by Helium dilution method (TLC by He), quantitative imaging analysis of high resolution CT (HRCT), 6 minute walk test (6MWT), and patient reported outcomes (PROs).

Subjects will be evaluated for study eligibility during Screening within 4 weeks before enrollment and Baseline assessments. Subjects, who are determined to be eligible, based on Screening assessments, will be enrolled in the study and randomly allocated to treatment with PRM-151 or placebo. Subjects will receive study drug treatment for at least 24 weeks. Approximately 60 subjects will be randomly assigned on a 2:1 basis to treatment with PRM-151 or placebo, as follows:

- PRM-151 10 mg/kg IV infusion over 60 minutes days 1, 3, and 5, then one infusion every 4 weeks
- Placebo IV infusion over 60 minutes on days 1, 3, and 5, then one infusion every 4 weeks

After completion of study treatment through Week 24, all subjects may receive PRM-151 10 mg/kg IV infusion over 60 minutes days 1,3, and 5, and then one infusion every 4 weeks for up to an additional 96 weeks in an open label study extension.

Study Duration:
Subjects will receive study drug for a minimum of 24 weeks.
Subjects will participate in the study for up to 128 weeks, including a 4-week screening period, 24-week treatment period, and a 96-week open-label treatment extension period and a 4-week follow up visit.

Study Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Subject is aged 40-80 years.
2. Subject has IPF satisfying the ATS/ERS/JRS/ALAT diagnostic criteria (Raghu, Collard et al. 2011). In the absence of a surgical lung biopsy, HRCT must be "consistent with UIP" defined as meeting either criteria A, B, and C, or criteria A and C, or criteria B and C below:
    - **A.** Definite honeycomb lung destruction with basal and peripheral predominance.
    - **B.** Presence of reticular abnormality AND traction bronchiect as is consistent with fibrosis, with basal and peripheral predominance.
    - **C.** Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern.
3. If on pirfenidone, subject must have been on a stable dose of pirfenidone for at least 3 months without increase in FVC% predicted on two consecutive PFTs, including screening PFTs.
4. If not currently receiving pirfenidone, subject must have been off pirfenidone for ≥ 4 weeks before baseline.
5. Subject has a FVC ≥50% and ≤ 90% of predicted.
6. Subject has a DL_{CO} ≥25% and ≤ 90% of predicted.
7. Minimum distance on 6MWT of 150 meters.
8. Subject has a forced expiratory volume in 1 second (FEV_1)/FVC ratio >0.70 post-bronchodilator.
9. Women of child bearing potential (WCBP), defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if ≤55 years or 12 months if >55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use adequate methods of birth control throughout the study. Adequate methods of contraception include use of oral contraceptives or Depo-Provera, with an additional barrier method (diaphragm with spermicidal gel or condoms with spermicide), double-barrier methods (diaphragm with spermicidal gel and condoms with spermicide), partner vasectomy, and total abstinence.
10. Subject has a life expectancy of at least 9 months
11. Subject, according to the investigator's best judgment, can comply with the requirements of the protocol.
12. Subject has provided written informed consent to participate in the study.

Exclusion Criteria:

1. Subject has emphysema ≥50% on HRCT or the extent of emphysema is greater than the extent of fibrosis according to reported results from the most recent HRCT.
2. Subject has a history of cigarette smoking within the previous 3 months.
3. Subject has received investigational therapy for IPF within 4 weeks before baseline.
4. Subject has received nintedanib within the 4 weeks before baseline.
5. Subject is receiving systemic corticosteroids equivalent to prednisone > 10 mg/day or equivalent within 2 weeks of baseline.
6. Subject received azathioprine, cyclophosphamide, or cyclosporine A within 4 weeks of baseline.
7. Subject has a history of a malignancy within the previous 5 years, with the exception of basal cell skin neoplasms. In addition, a malignant diagnosis or condition first occurring prior to 5 years must be considered cured, inactive, and not under current treatment.
8. Subject has any concurrent condition other than IPF that, in the Investigator's opinion, is unstable and/or would impact the likelihood of survival for the study duration or the subject's ability to complete the study as designed, or may influence any of the safety or efficacy assessments included in the study.
9. Subject has baseline resting oxygen saturation of < 89% on room air or supplemental oxygen.
10. Subjects that are unable to refrain from use of the following:
    a) Short acting bronchodilators on the day of and within 12 hours of pulmonary function, DL_{CO}, and 6 minute walk assessments.
    b) Long acting bronchodilators on the day of and within 24 hours of these assessments.
11. Subject has a **known** post-bronchodilator (short-acting beta agonist [SABA] – albuterol or salbutamol) increase in FEV_1 of >10% and in FVC of >7.5%.

Efficacy Assessments:

Treatment Period: Efficacy related Assessments

Subjects undergo testing on an every 4 week basis after randomization (occurring at Weeks 4, 8,12,16,20, 24 and 28) for efficacy and safety.

During treatment, PFTs, 6MWT, and PROs will be performed on an every 4 week basis. HRCT will be performed on Day 1 as the Baseline assessment and again at the completion of treatment at week 28. HRCT and PFTs must be done on the same day. PFTs will be reviewed centrally by reviewers blinded to treatment group and time point.

Order of Events

On assessment days, the order of events will be as follows:

- Vital Signs and PROs
- Full physical exam at Screening and an abbreviated physical exam thereafter
- Pulmonary function
  - Spirometry
  - Diffusion capacity only at Screening, Baseline and Week 28
  - TLC by helium dilution method only at Screening, Baseline and Week 28

- HRCT with spirometry only at Baseline and Week 28
- 6MWT
- Blood draw for tolerability/safety assessments and optional blood draw for exploratory biomarkers
- PRM-151 dosing

On loading dose days (3 and 5 of Week 0), the order of events will be as follows:

- Vitals signs and adverse event assessment
- PRM-151 dosing

Open Label Post-Study Treatment Extension

After completing 24 weeks of treatment, all subjects will be offered the option to receive PRM-151 in an open-label PRM-151 treatment extension period for up to 96 additional weeks. All subjects will receive PRM-151 treatment on Days 1, 3 and 5 of the first week of treatment in the extension. PROs, PFTs, and 6MWT will be done every 4 weeks for the first 24 weeks and then every12 weeks and DLco, FRC & TLC by He and HRCT will be done at 1.5 years (Week 76) and 2.5 years (Week 128).

SafetyAssessments:

Treatment Period: Tolerability/Safety-Related Assessments

Adverse events (AEs) and concomitant medications will be assessed at all study visits. In addition, information regarding hospitalizations, emergency department visits, and unscheduled or urgent care visits to a health care provider due to a deterioration in respiratory status or symptoms will be collected at all study visits.

Statistical Methods:

Continuous variables will be summarized by dose group with descriptive statistics (e.g., number of observations, mean, SD, median, interquartile range, maximum, and minimum). Categorical variables will be tabulated by frequency of subjects per dose group. Efficacy evaluations will be performed using the Full Analysis Set (FAS), defined as all subjects with a Baseline and at least 1 post-Baseline observation for each respective efficacy endpoint. A per-protocol analysis may be carried out based on exclusion of data from the FAS for major protocol violations; details will be included in the Statistical Analysis Plan (SAP). Safety evaluations will be based on the Safety Population, defined as all subjects who receive at least 1 dose of study drug and have a post-Baseline safety observation. Demographic data will be summarized for all subjects entering the study, and if material differences exist, for the FAS and Safety analysis datasets. (Additional details will be included in the SAP.)

Analyses will be based on observed data only; no data will be imputed.

The comparison of PRM-151 with placebo will be carried out via 2-sided statistical tests at alpha=0.05. The primary parameter will be tested with analysis of covariance (ANCOVA), with change from baseline to 28 weeks in FVC% predicted as dependent variable (outcome), and treatment, stratum, and treatment by stratum interaction as explanatory variables. Baseline FVC% predicted may be added as a covariate if appropriate.

AEs will be coded by using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number and percent of AEs reported, the number of subjects reporting each AE, and the number of subjects with any AE. A by-subject AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Safety data, including laboratory evaluations and vital signs assessments, will be summarized

by time of collection and by treatment group. In addition, change from Baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. The frequency of subjects with abnormal safety laboratory results will be tabulated by treatment.

Sample Size Considerations:
Approximately 60subjects are to be enrolled, of whom 40 subjects are to receive PRM-151 and 20 to receive placebo.
The primary objective is to demonstrate the efficacy of PRM-151 over placebo on absolute change from baseline to 28 weeks in mean FVC% predicted, hereafter referred to as the primary parameter. The primary parameter will be tested in a model with two types of subjects: subjects on a stable dose of pirfenidone, and subjects not on other treatment for IPF. The sample size is based on the following assumptions:

- Primary parameter is normally distributed
- Homogeneity of variance, i.e. the standard deviation is the same in both arms, and for both types of subjects.
- PRM-151: placebo equals 2:1.
- Expected value of the primary parameter for subjects on pirfenidone will be -1.5.
- Expected value of the primary parameter for subjects on no other treatment will be -3.
- Expected value of the primary parameter for subjects on PRM-151 will be ≥ 2.
- Standard deviation of the primary parameter is 5
- 75% of subjects will be on a stable dose of pirfenidone
- 25% of subjects will not be on other treatment for IPF
- Significance level (α)=0.05
- Desired power to demonstrate superiority is 80%

A sample size of sixty (60) subjects in total (40 PRM-151 and 20 placebo) is enough to demonstrate superiority at $P<0.05$ with a power of 80%. Stratified randomization will ensure a balance of PRM-151: placebo in both types of subjects.

Date of Original Protocol: Version 1.0 11 November 2014

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LIST OF ABBREVIATIONS

Abbreviation	Term
6MWD	6-Minute walk distance
6MWT	Six-minute walk test
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
ALAT	Latin American Thoracic Association
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC_{0-24}	Area under the curve from time 0 to 24 hours
$AUC_{0-\infty}$	Area under the curve from time 0 extrapolated to infinity
BAL	Bronchoalveolar lavage
BID	Twice daily
BRT	Bronchodilator reversibility testing
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CTGF	Connective tissue growth factor
DL_{CO}	Diffusion Capacity of Carbon Monoxide
DMC	Data Monitoring Committee
EC	Ethics Committee
ECM	Extracellular matrix
eCRF	Electronic case report form
ERS	European Respiratory Society
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
hPTX-2	Human pentraxin-2
HRCT	High-resolution computed tomography
hSAP	Human serum amyloid P(synonymous with hPTX-2)
IC	Inspiratory capacity
ICAM-1	Intercellular adhesion molecule-1

Abbreviation	Term
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL	Interleukin
IND	Investigational New Drug Application
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IV	Intravenous
JRS	Japanese Respiratory Society
LOXL2	Lysyl oxidase-like 2 protein
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
Mreg	Regulatory macrophages
mRNA	Messenger ribonucleic acid
O_2	Oxygen
PDGF	Platelet-derived growth factor
PFT	Pulmonary function test
PK	Pharmacokinetics
pp	Percentage points
PRO	Patient Reported Outcome
PTX-2	Pentraxin-2
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
SABA	Short-acting beta agonist
SAE	Serious adverse event
SAP	Serum amyloid protein, also Statistical Analysis Plan
SD	Standard deviation
SD-SOBQ	San Diego-Shortness of Breath Questionnaire
SGRQ	St. George Respiratory Questionnaire
SP-D	Surfactant protein D
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
TK	Toxicokinetic
TWA	Time-weighted average

Abbreviation	Term
UK	United Kingdom
US	United States
VCAM-1	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
WBC	White blood cell

1. INTRODUCTION

1.1. Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a rare, specific form of chronic, fibrosing, interstitial pneumonia limited to the lung. In the United States (US), IPF is estimated to affect up to 135,000 individuals, with approximately 50,000 cases being diagnosed annually (Raghu, Weycker et al. 2006). It is estimated that each year, 40,000 people in the US die due to IPF or complications thereof (Raghu, Weycker et al. 2006), the same as for breast cancer. There is limited information regarding the incidence and prevalence of IPF in the European Union (EU); however, it is estimated that up to 40,000 individuals are affected, with 5,000 cases diagnosed annually in the United Kingdom (UK) alone (Navaratnam, Fleming et al. 2011). IPF incidence and prevalence increase with age and are higher among males (Nalysnyk, Cid-Ruzafa et al. 2012). Overall, it is estimated that worldwide, 5 million individuals may be affected(Meltzer and Noble 2008). Although rare, the incidence of IPF is increasing, likely due to an increasing understanding of the disease and the recent development of uniform diagnostic criteria (Nalysnyk, Cid-Ruzafa et al. 2012)

IPF is a progressive disease with significant morbidity and mortality. The precise initiating injury is unknown, and the clinical course of IPF is variable. The fibrosis that develops in IPF follows a similar path to normal wound healing, but is progressive and without resolution. 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 alveoli. 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.

Ultimately, IPF leads to death, with a median survival after diagnosis of 3 years and a 5-year survival rate of 20% to 40%(Gomer and Lupher 2010). Estimates are that IPF is the primary cause of death for 60% of subjects 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).
No cure currently exists for IPF. There are two approved therapies in the United States and one in Europe. Pirfenidone was approved in the EU on February 28, 2011, for treatment of mild to moderate idiopathic pulmonary fibrosis (IPF), based on a statistically significant reduction in the decline of percent predicted FVC from Baseline at Week 72 ($p=0.001$) in patients receiving pirfenidone compared with patients receiving placebo.

Pirfenidone received approval in the US on October 15, 2014, for treatment of Idiopathic Pulmonary Fibrosis, based on the previous data and a new Phase 3 study, which demonstrated a statistically significant treatment effect of pirfenidone compared to placebo in change in %FVC from baseline to Week 52, with the proportion of patients declining being lower on pirfenidone than on placebo. Nintedanib was approved in the US on October 15, 2014, for Idiopathic Pulmonary Fibrosis, based on a statistically significant reduction in the annual rate of decline of FVC (in mL) in patients receiving nintedanib compared to patients receiving placebo in 3 clinical trials.

As effective treatment options for IPF have been limited until recently, affected subjects also receive supportive therapies and palliative care. As the clinical course of IPF is variable, strategies to treat the disease are individualized, based on the patient's medical history and clinical condition. Such treatments may include long-term oxygen (O_2) therapy; pulmonary rehabilitation; opiates; anti-reflux therapy; and low dose corticosteroids to treat cough. Although such therapies may ameliorate subjects' symptoms and improve comfort, they do not slow the progression of the disease or prolong survival. One exception is lung transplantation, which may be considered for subjects at increased risk of mortality, leads to an improvement in 5-year survival post-transplantation to 50 to 56% (Raghu, Collard et al. 2011).However, transplantation is generally recommended for subjects aged <60 years and, given that IPF is primarily a disease of the elderly with a mean age at diagnosis of 74 years (Fernandez Perez, Daniels et al. 2010), most subjects do not fall into a group for which transplant is a likely option.

1.2. PRM-151

Pentraxin-2 (PTX-2), also called serum amyloid P (SAP), is an endogenous protein that circulates in the bloodstream. 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 on monocytes and promotes their differentiation into regulatory macrophages (Mreg), 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. Both increased fibrocyte numbers in circulation (Moeller, Gilpin et al. 2009) and decreased levels of circulating PTX-2(Murray, Chen et al. 2011)have been characterized in IPF subjects relative to healthy subjects.

PRM-151 is a recombinantly-expressed version of human pentraxin-2 (hPTX-2). Like the native human protein, PRM-151 is expressed and purified as a non-covalent, homo-pentameric glycoprotein. Each monomer in the pentamer is comprised of 204 amino acids with one N-linked glycosylation site at Asn32 possessing a typical complex biantennary structure. There is one intramolecular disulfide bond between the only 2 cysteine residues in each monomer: Cys36-Cys95. The average molecular weight of the fully glycosylated, sialylatedpentamer is 127313 Da.

Preclinical and clinical data exist to support the investigation of PRM-151 in the treatment of fibrotic diseases.

1.2.1. Preclinical Pharmacology

Following the initial *in vitro* discovery by Gomer and Pilling suggesting that PTX-2 may regulate monocyte differentiation into spindle shaped fibrocytes(Pilling, Buckley et al. 2003), they, with others, published several studies on the activity of species-specific serum-derived PTX-2 in preventing fibrosis in models of bleomycin-induced lung fibrosis in rats and mice and also in a model of ischemia reperfusion injury to mouse heart(Pilling, Roife et al. 2007),(Haudek, Xia et al. 2006). Promedior and its collaborators have expanded the animal fibrosis model data using human serum-derived PTX-2 and PRM-151 to demonstrate potent anti-fibrotic activity in models of lung injury, skin injury, kidney injury, liver injury, radiation-induced injury, and a rabbit trabeculectomy model of eye injury.

1.2.2. Nonclinical Metabolism and Pharmacokinetics

The half-life ($t_{1/2}$) of IV-dosed PTX-2/PRM-151 (2-7 mg/kg) has been calculated for multiple species, with the following results: mouse (4-8 hr) < rabbit (7.3 hr) < monkey (6-15 hr) < rat (13-23 hr) < human (30 hr, [human $t_{1/2}$ from Promedior single, ascending dose study, PRM151A-11EU; 10 mg/kg dose in healthy volunteers])(Hawkins, Wootton et al. 1990).

Toxicokinetics (TK) in the rat and monkey 14-day repeat IV-dose studies showed dose-proportional increases in systemic exposure, with slight to moderate increases in exposure with multiple dosing. Anti- PRM-151 antibodies were detected following multiple doses, but did not appear to affect the TK parameters in these studies. In a 6 month toxicology study in rats, Cmax and AUC were dose proportional at baseline but not at later time points. Investigation of this phenomenon indicates that AUC at later time points is falsely low due to interference by ADA in the PK assay.

Following IV administration of radiolabeled PRM-151, the highest percentage of the administered dose was measured in the systemic tissues at 1 hr post-dose; the highest values were in the liver, kidneys, lung, and spleen. A CYP450 inhibition/stimulation study showed no inhibition of the 5 enzymes tested.

1.2.3. Toxicology

No adverse toxicological effects were observed in 14-day IV daily dose studies in Sprague Dawley rats at doses ranging from 10 to 200 mg/kg/day or in cynomolgus monkeys at doses ranging from 12 to 120 mg/kg/day. The no observed adverse effect level (NOAEL) of 14 daily IV doses of PRM-151 was set at ≥ 200 mg/kg in rats and ≥ 120 mg/kg in cynomolgus monkeys. Six month toxicology studies were initiated in Sprague Dawley rats and cynomolgus monkeys employing weekly dosing, and acute infusion reactions, some resulting in death, occurred in both studies beginning on Day 15. The infusion reactions in rats were managed by slowing the rate of infusion and reducing

the highest dose from 200 to 150 mg/kg, and the study continued to completion, with a NOAEL of 100 mg/kg based on a death of one rat unrelated to an acute infusion reaction at the 150/200 mg/kg dose. There were also adverse findings of liver fibrosis at the 150/200 mg/kg dose level. The monkey study was terminated early after a death at the lowest dose level due to an infusion reaction. The acute infusion reactions were determined to be secondary to complement activation by anti-drug antibodies to PRM-151, a human protein foreign to both test species.

Reproductive and developmental toxicity studies have not been conducted with PRM-151. Increased testes weights were observed in a mouse dose range-finding study, but the relationship to test article administration could not be determined due to the small number of animals in the study. However, no treatment-related findings (organ weights or histopathology) were identified in the reproductive organs of rats or cynomolgus monkeys in the 14-day or rats in the 6 month IV dose toxicology studies. Women of childbearing potential will be required to take precautions to prevent pregnancy in the current study.

As noted above, PRM-151 is immunogenic in non-human species. Phenotypes of deficient or knockout mice may identify potential consequences of PRM-151-induced neutralizing or depleting antibodies to hPTX-2. To date, there has been no toxicity associated with complete deficiency of PTX-2 in mice (Gillmore, Hutchinson et al. 2004), and therefore the toxicity risks due to generation of depleting or neutralizing antibodies to PRM-151 or hPTX-2 are considered low.

PRM-151 is dose equivalent in humans and non-human species, and the dose of 10 mg/kg selected for the current study has a safety margin of 10 compared to the rat NOAEL of 100 mg/kg. Moreover, the NOAEL in rats was based on 10 mg/kg every week with a total of 2600 mg/kg in 26 weeks, whereas humans are being dosed at 10 mg/kg days 1, 3, and 5 and then every 4 weeks for a total of 90 mg/kg in 24 weeks.

1.2.4. Clinical Experience in Healthy Subjects and Subjects with IPF and Myelofibrosis (MF)

PRM-151 administered IV has been investigated in 18 healthy subjects and in 18 subjects with IPF. PRM-151 is being investigated in an ongoing Phase 2 study in subjects with MF in which 27 subjects enrolled, 20 subjects completed 24 weeks of treatment, and 10 subjects have received at least 36 weeks of treatment in a study extension.

In a single ascending dose study (PRM151A-11EU), there were no dose limiting toxicities and no serious adverse events (SAEs) were noted. The most frequent (≥15%) treatment-emergent adverse events (TEAE) for the PRM-151-treated subjects were fatigue (38%) and headache (19%). Overall, the data indicate that single doses of 0.1, 0.25, 0.5, 1, 2, 5, 10, and 20 mg/kg were safe and well tolerated. The $t_{1/2}$ of IV

administered PRM-151 was approximately 30 hours. The PK profile of PRM-151 was linear and similar in healthy subjects and subjects with IPF.

In a multiple ascending dose study (PRM151F-12GL), 21 subjects with IPF were enrolled in successive cohorts of 7 subjects each, randomized 5:2 to receive either PRM-151 or placebo. Each cohort was assigned a progressively increasing dose level of PRM-151: 1, 5, or 10 mg/kg administered IV on Days 1, 3, 5, 8 and 15. Subjects in all 3 PRM-151 dose groups demonstrated improvement in FVC% predicted at Day 57 after receiving PRM-151 on Days 1, 3, 5, 8 and 15. Mean change from Baseline in FVC% predicted at Day 57 was + 2.4 (standard deviation [SD] 3.8) for all PRM-151-treated subjects versus -1.5 (SD 3) for placebo-treated subjects (p=0.0524). Furthermore, 6 out of 14 PRM-151 treated subjects experienced a relative increase from Baseline of at least 5% in FVC % predicted. Review of other pulmonary function tests (PTFs) showed an increase from Baseline in forced expiratory volume in 1 second (FEV_1) in all 3 dose groups, whereas a decrease from Baseline was seen in the placebo group; none of the between group differences was statistically significant. Mean PFTs at Baseline and change from Baseline on Day 57 are summarized inTable1-1.

Table 1-1: Mean (SD) Pulmonary Function Tests at Baseline and Change from Baseline to Day 57: Study PRM-151F-12GL

		PRM-151			
Parameter	**Placebo (N=6)**	**1 mg/kg (N=5)**	**5 mg/kg (N=5)**	**10 mg/kg (N=4)**	**All Doses (N=14)**
FVC (liters)					
Baseline	2.2 (0.64)	3.0 (0.85)	2.8 (0.73)	3.0 (0.71)	2.9 (0.71)
Δ from Baseline	-0.06 (0.116)	0.06 (0.164)	0.06 (0.074)	0.08 (0.210)	0.06 (0.142)
FVC % predicted (%)					
Baseline	63 (16.7)	82 (15.5)	80 (7.8)	73 (14.3)	79 (12.5)
Δ from Baseline	-1.5 (3.3)	2.4 (4.6)	2.8 (3.0)	1.8 (5.3)	2.4 (4.0)
DL_{CO} (%)					
Baseline	35 (8.4)	41 (10.5)	53 (9.8)	46 (7.2)	47 (10.1)
Δ from Baseline	-2.3 (2.1)	0.2 (3.3)	-4.0 (6.8)	-1.5 (3.8)	-1.8 (4.9)
FEV_1 (%)					
Baseline	69 (17.7)	86 (16.8)	87 (11.9)	73 (12.1)	83 (14.3)
Δ from Baseline	-1.7 (4.3)	2.6 (4.3)	2.4 (1.1)	0.3 (3.8)	1.9 (3.2)

Results of the 6-minute walk test (6MWT) showed that on Day 57, the distance walked was decreased from Baseline by a mean of -11 (SD, 51) meters in the placebo group compared with a numerical improvement in each of the 5 mg/kg, 10 mg/kg, and all dose combined groups [+6 (SD, 43), +35 (SD, 45), and +8 (SD, 51) meters, respectively], although these differences were not statistically significant. No infusion reactions, no

dose-limiting toxicity and no serious adverse events were observed. In addition, no antibodies to PRM-151 were measured. In the PRM-151-treated subjects, the most common adverse events recorded during the study were cough (n = 7; 47%), productive cough (n=4; 27%) followed by fatigue (n = 3; 20%) and headache (n = 3; 20%). The incidence of these events was comparable in the placebo group [cough, 33% (n = 2); productive cough, 33% (n = 2); fatigue, 17% (n = 1) and headache, 17% (n = 1)]. Neither the nature nor the frequency of these reported adverse events increased with ascending PRM-151 dose levels. One subject in the 1 mg/kg dose group experienced an episode of moderate hypotension and dizziness just before administration of the third dose of PRM-151. These symptoms were considered possibly related to PRM-151 administration, and resulted in discontinuation of PRM-151 treatment for that specific subject.

In a Phase 2 study in subjects with myelofibrosis treated with PRM-151 either weekly or every 4 weeks, either alone or added to a stable dose of ruxolitinib, data on all 20 subjects who completed 24 weeks of treatment and 10 who have completed at least 36 weeks of treatment as of Sept. 29, 2014 have demonstrated reduction in bone marrow fibrosis in 9 subjects and improvement in anemia and/or thrombocytopenia in 9 subjects, 5 of whom also had bone marrow improvement. Treatment emergent adverse events have been mostly mild (Grade 1 or 2 by the CTCAE criteria) and unrelated to PRM-151. Hyperlinks to the CTCAE criteria are available in Appendix H. There were 2 instances of infusion reactions (Grade 2); in each case, subsequent treatments were uneventful with diphenhydramine and dexamethasone administered prior to treatment. There were 5 serious adverse events (SAEs) considered possibly related, including 1 death. These included abdominal pain (recovered), sialadenitis (recovered), respiratory syncytial virus (recovered), and gastroenteritis (norovirus documented in entire family) and pneumonia (death). There were two unrelated deaths including pneumonia (subject voluntarily discontinued all medications including antibiotics and subsequently died) and multi-organ failure and cardiac arrest (automatic implantable cardioverter defibrillator failed) after bone marrow biopsy site hematoma in a subject with a pre-existing arrhythmia. In summary, reported adverse events have been consistent with morbidity and mortality expected in this patient population and with adverse events reported in the treatment and placebo arms of ruxolitinib clinical trials(Verstovsek, Mesa et al. 2012).

Based on these encouraging data, Promedior has planned the current study to investigate the effects of PRM-151administered through Week 24 to a population of subjects with IPF.

1.3. Quantitative Imaging

This study incorporates two quantitative imaging techniques to assess the degree of change in pulmonary fibrosis. Background information for each technique is provided below:

1.3.1. **Imbio**

ImbioLung Texture Analysis classifies each voxel of lung parenchyma based on morphology and density characteristics into Normal, Interstitial Lung Abnormality (ILA) categories of Ground glass, Reticular, and Honeycombing; and Low Attenuation (mild, moderate, severe). It quantifies these characteristics by total volume (cm^3) or % total lung volume. Requirements for optimal use of Imbio technology include inspiratory non-contrast enhanced HRCT (images obtained at TLC), volumetric scans with slice thickness ≤ 5mm (ideally less than 2mm), and CT data that has not been modified by edge enhancement filters as part of the reconstruction process. Previous studies have shown that quantification of lung parenchyma by Imbio Lung Texture Analysis is comparable to but more reproducible than radiologist assessment (Zavaletta, Bartholmai et al.), that these parameters correlate with known markers of disease severity such as FVC%, DLCO, 6MWT[2] and GOLD classification (Raghunath 2014) and that changes in ILA features over time are predictive of mortality in UIP(Maldonado, Moua et al.). The Lung Texture Analysis software was previously utilized for quantitative evaluation of HRCT data in greater than 4000 ILD and COPD subjects within the NHLBI/NIH-funded Lung Tissue Research Consortium effort.

1.3.2. **FluidDA**

With FluidDA functional respiratory imaging (FRI) technology, HRCT images are used to construct 3-D models to measure lobar volume, lung volume, airway volume, internal lobar airflow distribution, and airway resistance. Requirements for optimal use of FluidDA technology include inspiratory and expiratory scans (images obtained at both TLC and FRC, spirometry on CT table to confirm that TLC and FRC are optimal, consistent image reconstruction algorithms, and volumetric scans with slice thickness ≤ 1mm. Previous studies in COPD and asthma have shown that FRI is 3-8x more sensitive than PFTs to evaluate treatment (De Backer, Vos et al.), and that changes in FRI parameters correlate with changes in lung function and subject symptoms. IPF is a new area of exploration for FluidDA, but the technique appears promising.

1.3.3. **Retrospective Quantitative Imaging Analysis of PRM-151 Data**

Both Imbio Lung Texture Analysis and FluidDA FRI techniques were applied retrospectively to HRCT obtained at screening and Day 57 in Study PRM151f-12GL. Limitations of retrospective analysis included lack of inspiratory and expiratory images for some subjects, the fact that only reconstructed images of variable slice thickness, reconstruction kernel and temporal correlation with the physiologic tests were available, and the fact that slice thicknesses were ≥ 5 mm for some subjects. CALIPER results were reported as change from screening to Day 57 in % total lung volume occupied by interstitial lung abnormality (ILA= groundglass plus reticular plus honeycombing) and non-interstitial lung abnormality (non-ILA=normal plus mild low attenuation).Analysis with FRI was restricted to lobar volumes, with results were reported as change from screening to Day 57 in the sum of the percent predicted lobar volumes. Quantitative imaging data was analyzed in 16 subjects who had ≤ 36 days between screening CT and Day 1 PFTs. There was a strong negative correlation between baseline FVC % predicted

and percent of lung volume identified as ILA by CALIPER. Non-ILA lung (normal + mild low attenuation) decreased in all placebo subjects and was stable or increased in 5 PRM-151 treated subjects, all of whom had stable or increased FVC % predicted. There was no clear correlation between the magnitude of change in FVC% predicted and %Non-ILA, possibly due the limitations inherent to retrospective analysis of the HRCT data. The analysis was confounded in 4 subjects by poor inspiratory effort for the HRCT series that should have been performed at TLC on the Day 57. Lobar volumes were stable or increased by FluidDA measurement in 8 PRM-151 treated subjects, 5 of whom had stable to increased FVC % predicted.

1.4. Rationale for Current Study

IPF is a progressive disease that leads to significant morbidity and mortality, with a median survival after diagnosis of 3 years and a 5-year survival rate of 20 to 40% (Gomer and Lupher 2010). Despite the two recently approved therapies, no therapies have yet been developed for IPF that meaningfully reverse the progressive lung fibrosis that is the basic pathologic feature of the disease and no therapies have reproducibly demonstrated an improvement in lung function. IPF remains a progressive disease with no cure other than lung transplant in selected patients. Thus, there is still a significant unmet medical need for subjects with IPF, particularly those with severe disease (Nalysnyk, Cid-Ruzafa et al. 2012).

As summarized previously, encouraging efficacy data were obtained in a Phase 1 study of PRM-151 in a relatively small number of subjects with IPF (n=15) who received PRM-151 administered via 30-minute IV infusion at doses of 1, 5, and 10 mg/kg on Days 1, 3, 5, 8, and 15, with all 3 groups demonstrating improvement in FVC % predicted at Day 57. Furthermore, 6 out of 14 PRM-151 treated subjects experienced a relative improvement of at least 5% from Baseline in FVC % predicted. These results seen at 8 weeks post-Baseline after 5 PRM-151 doses administered over 2 weeks are encouraging, particularly considering that the best result with pirfenidone and nintedanib is a reduction in the rate of decline rather than improvement in FVC (King, Bradford et al.; Richeldi, du Bois et al.). Improvements from Baseline were also observed in FVC measured in milliliters and in 6MWT distance for PRM-151-treated subjects. Review of safety data from this study demonstrated that PRM-151at doses up to 10 mg/kg were safe and well tolerated in subjects with IPF. No SAEs were observed over 57 days, and similar types and number of TEAEs were reported in both PRM-151- and placebo-treated subjects.

Based on these encouraging data in a small cohort of subjects with IPF, Promedior has planned to investigate the effects of PRM-151 in the proposed study involving a larger population of subjects with this condition.

1.5. Risk/Benefit Assessment

PRM-151, a recombinant form of an endogenous human protein, has been well tolerated in preclinical toxicology studies and Phase 1 and 2 clinical studies, and has shown an early trend towards efficacy in subjects with IPF. Based on encouraging Phase 1 data in subjects with IPF, PRM-151 has the potential to be a safe, disease modifying treatment for a broad spectrum of fibrotic diseases, including IPF.

PRM-151 represents the recombinant version of an endogenous human serum protein, and as such was predicted to have a very favorable safety index. This prediction has been confirmed in multiple preclinical and clinical studies to date. Two Phase 1 studies of PRM-151 administered IV to normal volunteers and IPF subjects have been completed, with no SAEs reported and no other safety signals seen. The single ascending dose study (PRM151A-11EU) tested dose levels as high as 20 mg/kg. The multiple ascending dose study (PRM151F-12GL) demonstrated that PRM-151 administered by 30 minute IV infusion on Days 1, 3, 5, 8 and 15 at up to 10 mg/kg was safe and well tolerated in subjects with IPF, with no SAEs noted in 57 days; similar types and number of TEAEs were reported in both PRM-151 and placebo treated subjects. Safety data from 27 patients with MF, including 24 weeks of safety data in 20 subjects and an additional 12 weeks of safety data in 10, confirms the excellent safety profile of PRM-151 to date. Most adverse events have been Grade 1 or 2 and unrelated to PRM-151, and 5 possibly related SAEs, including one death, have been reported in a group of older patients (median age 67 years) with a serious, life threatening disease.

Risks associated with PRM-151 are inherent in its being the recombinant form of a naturally occurring human protein, and consist of potential development of anti-drug antibodies and infusion reactions. PRM-151 has an endogenous counterpart, and, therefore, anti-drug antibodies could develop that could potentially affect the efficacy of PRM-151 treatments in addition to having the potential to cross-react with endogenous hPTX-2. Anti-drug antibodies were detected in 3 subjects in the MF trial, with no apparent impact on pharmacokinetics, safety, or efficacy. Two subjects had mild infusion reactions which were easily managed and prevented in the one subject that was rechallenged; anti-drug antibody was detected in one of them.

PRM-151 is not a general immunosuppressant, and treatment with PRM-151 is not expected to increase rates of infection or adversely affect wound healing.

As with any protein therapeutic, the potential for reactions exists and safety procedures will be implemented including careful monitoring of subjects during infusions and of infusion sites. Appropriate personnel, medication, and other requirements for the treatment of potential infusion reactions will be required by the protocol.

PRM-151 is an investigational agent. Subjects are not anticipated to derive direct benefit from participation in studies; the potential benefits of PRM-151 as a therapy for IPF remain to be proven in clinical efficacy studies.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of this study are:

- To demonstrate the superiority of PRM-151 to placebo in preservation or increase from baseline to 28 weeks in mean FVC% predicted in subjects on a stable dose of pirfenidone and subjects not on other treatment for IPF.

2.2. Secondary Objectives

The secondary objectives of this study are:

- To demonstrate the superiority of PRM-151 to placebo in preservation or increase from baseline to 28 weeks in normal lung as quantified by structural imaging in subjects on a stable dose of pirfenidone and subjects not on other treatment for IPF.
- To assess the tolerability and safety of PRM-151 in subjects with IPF treated for 24 weeks
- To assess the ability of PRM-151 to reduce disease-related events associated with mortality
- To assess the ability of PRM-151 to preserve or increase 6 minute walk distance

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To assess the ability of PRM-151 to preserve or increase gas exchange
- To assess the impact of PRM-151 on disease related symptoms
- Assess the impact of PRM-151 on functional respiratory imaging parameters
- Assess the impact of PRM-151, disease pathogenesis and disease progression on exploratory serum, cellular and genetic biomarkers

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint for the study is:

- Mean absolute change from baseline in FVC % predicted from baseline to week 28.

3.2. Secondary Endpoints

The secondary endpoints for the study are:

1. **Structural Imaging**:
    - Mean absolute change from baseline at 28 weeks in total lung volume and volume of parenchymal features (normal, ground glass density, reticular changes, honeycombing, and low attenuation areas) using quantitative imaging software to measure absolute volume (in ml) and relative % of total lung volume.
    - Transitions between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and low attenuation areas) by quantitative software.

2. **Safety**: Tolerability/safety will be assessed over the 24 week dosing period by the following parameters:
    - Incidence of AEs.
    - Incidence of serious adverse events (SAEs).
    - Incidence of respiratory AEs and SAEs.
    - Proportion of subjects discontinuing study drug due to AEs.
    - Change from Baseline in hematology and serum chemistries.
    - All-cause mortality.
    - Mortality due to respiratory deterioration.
3. **Disease related events associated with mortality**: The number of "respiratory decline" events over the 6 month dosing period as defined below:
    - Unscheduled visits to a healthcare professional for respiratory status deterioration.
    - Urgent care visit for respiratory status deterioration.
    - Hospitalization due to a worsening or exacerbation of respiratory symptoms.

All "respiratory decline" events will be further characterized according to the definitions of IPF-related disease exacerbation, as defined according to American Thoracic Society (ATS) criteria (Raghu, Collard et al. 2011):

- Unexplained worsening of dyspnea over 1 month.
- Worsened or severely impaired gas exchange.
- New radiographic alveolar infiltrates.
- The absence of another reason for the worsening respiratory symptoms, (pulmonary embolism, congestive heart failure, pneumothorax).
- Acute, unexplained decline in oxygen saturation over 1 month.

4. **Pulmonary Function Tests**
    - Time-weighted average (TWA) of change in FVC% predicted from Baseline to Week 28.
    - TWA of change in FVC in ml from Baseline to Week 28.
    - Proportion (%) of subjects with an absolute decline in FVC% predicted of ≥5%and ≥10%from Baseline to Week 28.
    - Proportion (%) of subjects with an absolute decline in FVC in mls of 100ml and200mlfrom Baseline to Week 28.
    - Proportion of subjects with an absolute increase in FVC % predicted of ≥5% and ≥10% from Baseline to Week 28.
    - Proportion of subjects with an absolute increase in FVC in ml of 100ml and 200ml from Baseline to Week 28.
    - Mean absolute change from baseline to Week 28in % predicted Diffusion capacity of carbon monoxide (DLCO).
    - Change in 6-minute walk distance, in meters, from baseline to Week 28.

3.3. Exploratory Endpoints

The exploratory endpoints for the study include:

1. **Patient Reported Outcomes**
    - Change in Patient Reported Outcomes as measured by King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and Leicester Cough Questionnaire (LCQ) from baseline to week 28.
2. **Quantitative Functional Respiratory Imaging**
    - Changes from baseline to 28 weeks in regional lung volumes, specific airway volumes and resistance as measured by quantitative imaging software (FluidDA).
3. **Biomarkers**
    - Changes in serum and cellular biomarkers and response according to baseline genetic characteristics: including but not limited toTLR3 L412F polymorphism, MUC5B promoter polymorphism.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

The current study is a Phase 2, randomized, double-blind, placebo-controlled, pilot study designed to evaluate the efficacy and safety of PRM-151 administered for 24 Weeks to subjects with IPF. Subjects meeting the eligibility criteria for the study will be randomized to PRM-151 10 mg/kg every 4 weeks or placebo. Efficacy will be evaluated through pulmonary function tests (PFTs), high resolution CT (HRCT), 6 minute walk test (6MWT), and Patient Reported Outcomes (PROs).
Subjects will be evaluated for study eligibility during Screening within 4 weeks before enrollment and Baseline assessments. Subjects who are determined to be eligible, based on Screening assessments, will be enrolled in the study and randomly allocated to treatment with PRM-151 or placebo. Subjects will receive study drug treatment for 24 weeks.
Approximately 60 subjects will be randomly assigned on a 2:1 basis to treatment with PRM-151 or placebo, as follows:

- PRM-151 10 mg/kg IV infusion over 60 minutes on days 1, 3, and 5, then one infusion every 4 weeks
- Placebo IV infusion over 60 minutes on Week 0 Days 1, 3, and 5, then one infusion every 4 weeks

After completion of study treatment through Week 24, all subjects may receive PRM-151 10 mg/kg IV infusion over 60 minutes days 1,3, and 5, and then one infusion every 4 weeks for up to an additional 96 weeks in an open label study extension.

4.1.1. Treatment Period: Efficacy-related Assessments

Subjects undergo testing on an every 4 week basis after randomization (occurring at Weeks 4, 8,12,16,20 and 24) for efficacy and safety.

During treatment, PFTs, 6MWT, and PROs will be performed on an every 4 week basis. HRCT will be performed on Day 1 as the Baseline assessment and again at Week 28. HRCT and PFTs must be done on the same day. PFTs will be reviewed centrally by reviewers blinded to treatment group and time point.

4.1.2. Treatment Period: Tolerability/Safety-Related Assessments

Adverse events (AEs) and concomitant medications will be assessed at all study visits. In addition, information regarding hospitalizations, emergency department visits, and unscheduled or urgent care visits to a health care provider due to a deterioration in respiratory status or symptoms will be collected at all study visits.

4.1.3. Open Label Post-Study Treatment Extension

After completing 24 weeks of treatment, all subjects will be offered the option to receivePRM-151 in an open-label PRM-151 treatment extension period for up to 96 additional weeks. All subjects will receive PRM-151 treatment on Days 1, 3 and 5 of the first week of treatment in the extension. PROs, PFTs, spirometry and 6MWT will be done every 4 weeks for the first 24 weeks and then every 12 weeks. DLco, FRC &TLC by He will be

done every 12 weeks. HRCT will be done at 1.5 years (Week 76) and 2.5 years (Week 128) on the same day as DLco and FRC & TLC by He.

4.1.4. **Study Duration**

Subjects will receive study drug for a minimum of 24 weeks. Subjects will participate in the study for up to 128 weeks, including a 4-week screening period, 24 week treatment period, a 96 week open-label treatment extension period, and a 4 week follow up period.

5. SELECTION OF STUDY POPULATION

5.1. Study Population

5.1.1. Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

1. Subject must be 40-80 years of age at the time of signing the Informed Consent Form (ICF);
2. Subject has well documented IPF satisfying the ATS/ERS/JRS/ALAT diagnostic criteria (Raghu, Collard et al. 2011). In the absence of a surgical lung biopsy, HRCT must be "consistent with UIP" defined as meeting either criteria A, B, and C, or criteria A and C, or criteria B and C below:
    A. Definite honeycomb lung destruction with basal and peripheral predominance.
    B. Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance.
    C. Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern.
3. If on pirfenidone, subject must have been on a stable dose of pirfenidone for at least 3 months without increase in FVC% predicted on two consecutive PFTs, including screening PFTs.
4. If not currently receiving pirfenidone, subject must have been off pirfenidone for ≥4 weeks before baseline.
5. Subject has a FVC ≥50% and≤ 90%of predicted.
6. Subject has a DLCO ≥25% and≤ 90% of predicted.
7. Minimum distance on 6MWT of 150 meters.
8. Subject has a forced expiratory volume in 1 second (FEV_1)/FVC ratio >0.70 post-bronchodilator.
9. Women of child bearing potential (WCBP), defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if ≤55 years or 12 months if >55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use adequate methods of birth control throughout the study. Adequate methods of contraception include use of oral contraceptives or Depo-Provera, with an additional barrier method (diaphragm with spermicidal gel or condoms with spermicide), double-barrier methods (diaphragm with spermicidal gel and condoms with spermicide), partner vasectomy, and total abstinence.
10. Subject has a life expectancy of at least 9 months
11. Subject, according to the investigator's best judgment, can comply with the requirements of the protocol.
12. Subject has provided written informed consent to participate in the study.

5.1.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be rolled in the study:

1. Subject has emphysema ≥50% on HRCT or the extent of emphysema is greater than the extent of fibrosis according to the reported results of the most recent HRCT.
2. Subject has a history of cigarette smoking within the previous 3 months.
3. Subject has received investigational therapy for IPF within 4 weeks before baseline.
4. Subject has received nintedanib within the 4 weeks before baseline.
5. Subject is receiving systemic corticosteroids equivalent to prednisone > 10 mg/day or equivalent within 2 weeks of baseline.
6. Subject received azathioprine, cyclophosphamide, cyclosporine A within 4 weeks of baseline.
7. Subject has a history of a malignancy within the previous 5 years, with the exception of basal cell skin neoplasms. In addition, a malignant diagnosis or condition first occurring prior to 5 years must be considered cured, inactive, and not under current treatment.
8. Subject has any concurrent condition other than IPF that, in the Investigator's opinion, is unstable and/or would impact the likelihood of survival for the study duration or the subject's ability to complete the study as designed, or may influence any of the safety or efficacy assessments included in the study.
9. Subject has baseline resting oxygen saturation of < 89%on room air or supplemental oxygen.
10. Subject use of inhaled bronchodilator agents is allowed, but use of short acting agents is disallowed the day of and within 12 hours of pulmonary function, DL_{CO}, and 6 minute walk assessments. Use of long acting bronchodilators is disallowed the day of and within 24 hours of these assessments.
11. Subject has a known post-bronchodilator (short-acting beta agonist [SABA] – albuterol or salbutamol) increase in FEV_1 of >10%andin FVCof>7.5%.

5.2. Withdrawal and Replacement of Subjects

The Investigator may withdraw a subject from the study for any of the following reasons:

- Subject, Investigator, or Sponsor request.
- Protocol violation.
- AE.
- Pregnancy.
- Progression of disease that, in the opinion of the Investigator, precludes further study drug treatment.
- Subject decision. A subject may withdraw consent to participate in the study at any time.

The reason for study withdrawal is to be documented in the subject's source documents and electronic case report form (eCRF).

5.3. Study Termination

If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- Site-specific inability of an Investigator to enter subjects at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.
- A decision on the part of the Sponsor to suspend or discontinue the study for administrative reasons.

5.4. Subject Management

This study will be conducted on an outpatient basis.

Subjects will be evaluated for study eligibility during the Screening period within 4 weeks before the first study drug dose. All subjects must provide written informed consent before any study specific samples are collected or evaluations performed in this study.

Subjects who are determined to be eligible for the study will be enrolled and randomly assigned to treatment at Baseline (Week 0). For the purposes of this study, enrollment is defined as randomization.

During the 24-week treatment period, subjects are to attend study center visits on Days 1, 3 and 5 then an every 4-week basis at Weeks 4, 8, 12, 16, 20, and 24 (±3 days) for study-related efficacy assessments and dosing.

After completing treatment through week 24, subjects will be offered the option to continue PRM-151 in an open-labeled treatment extension for up to 96 additional weeks.

An End of Study visit is to be conducted 4 weeks (±3 days) after the last dose of study drug (Week 28 for the main study and Week 128 for the open label extension).

5.5. Investigator Compliance

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol.

5.6. Subject Adherence

All subjects are required to adhere to the protocol-specified visit schedule. If a subject misses a scheduled visit, attempts should be made to reschedule the visit within the visit

windows described above. Failure to attend scheduled study visits may result in discontinuation from the study.

5.7. Data Monitoring Committee

An unblinded DMC will be established to review safety data from this study, thereby better ensuring the safety of study participants. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will be constituted of independent clinicians expert in the field of IPF and clinical research. A formal charter will be established for the conduct of the DMC.

6. STUDY TREATMENT(S)

6.1. Investigational Product

All study drugs are for investigational use only and are to be used only within the context of this study. All study drugs will be supplied by Promedior.

6.2. Treatment(s) Administered

Subjects will be randomized to receive the study drug PRM-151 or placebo. Subjects randomized to placebo will receive intravenous (IV) infusions of sterile saline solution over 60 minutes. Please refer to the Pharmacy Manual for more detail.

Subjects randomized to study drug will receive intravenous (IV) infusions of 10 mg/kg PRM-151 over 60 minutes, with dose based on the subject's screening weight. Refer to the Pharmacy Manual and the Investigator's Brochure for detailed instructions on special precautions and handling and requirements for weight based dose recalculations.

On all dosing days, dosing will occur ***after*** all safety and efficacy assessments scheduled for that visit are completed

Medical personnel authorized by the Investigator will be responsible for the administration of study drug and for observation of each subject throughout the study. Subjects should be observed for one hour post infusion to monitor for infusion related reactions.

In the case of occurrence of signs and symptoms consistent with infusion related reaction, follow institutional protocol and reduce the rate of infusion of PRM-151 to half the initial rate; consider discontinuing infusion of PRM-151 if symptoms do not respond immediately to medical intervention. If signs and symptoms do not resolve immediately by slowing the infusion, discontinue infusion of PRM-151. If signs and symptoms resolve with intervention including discontinuation of PRM-151, PRM-151 infusion may be restarted at half the initial rate.

If PRM-151 resulted in an infusion related reaction, during a prior administration, use the following premedication for all subsequent PRM-151 administration:

a. Diphenhydramine 50 mg IV or clemastine 2 mg IV

b. Dexamethasone 10 mg IV

No other dose modifications are required per protocol. The investigator should use his/her medical judgment in the case of adverse events that may require a dose interruption.

6.3. Method of Assigning Subjects to Treatment Groups

Subjects who are candidates for screening into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria initially have been satisfied. The Unblinded Pharmacist will register the subject in the IVRS system, and the IVRS system will assign a sequential and unique subject number. Once a subject number has been assigned, it cannot be reused.

Prior to randomization, the Investigator will ensure that the subject continues to meet the inclusion and exclusion criteria and is eligible for study participation.

Once a subject is deemed by the Investigator to be eligible, the unblinded pharmacist will access the IVRS system for randomization and study drug assignment.

6.4. Blinding

All study personnel, with the exception of the unblinded site pharmacist, will be blinded to the treatment allocation a subject is randomized to. It is imperative that this blinding be maintained during the dispensing of investigational product.

6.4.1. Procedures for Breaking the Blind

The treatment assignment must not be broken during the study except in emergency situations where the identification of study drug is required for further treatment of the subject. Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, the Investigator should use his/her best judgment as to whether to unblind without first attempting to contact the Medical Monitor to discuss and agree to the need for unblinding. If the Investigator determines that it is not necessary to unblind immediately, he/she will first attempt to contact the Medical Monitor to discuss and agree to the need for unblinding. If the Investigator has tried but is unable to reach the Medical Monitor, he/she should use his/her best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the Medical Monitor.

6.5. Study Drug Supply

PRM-151 Solution for Injection is a 20 mg/mL solution of PRM-151 in 10 mM sodium phosphate, 5% (w/v) sorbitol, and 0.01% (w/v) polysorbate 20 with a pH of 7.5. Each vial of PRM-151 Solution for Injection contains 160 mg of PRM-151 in 8.0 mL of solution.

Placebo consists of an infusion of sterile physiologic saline, matched to PRM-151 in total volume.

6.6. Packaging and Labeling

PRM-151 is supplied in 10 ml single use vials as a clear to opalescent, sterile 20.0 mg/mL solution 10 mM sodium phosphate, 5% (w/v) sorbitol, and 0.01% (w/v) polysorbate 20 with a pH of 7.5. Each vial contains 8 ml PRM-151 (160mg of PRM-151).

Study drug will be labeled investigational. Study drug labels will not bear any statement that is false or misleading in any manner or represents that the study drug is safe or effective for the purposes for which it is being investigated.

6.7. Storage and Accountability

PRM-151 will be provided to the clinical site in a temperature controlled, monitored container. Investigational product should be stored under refrigerated conditions (2°C-8°C [35.6°F-46.4°F]) and protected from light. Vigorous mixing or vortexing should be avoided.

Investigational product will be dispensed at the study site and stored in a locked storage area. The disposition of all investigational product delivered to a Principal Investigator must be recorded on a subject-by-subject basis by completing the Clinical Trial Material Accountability Log. The date and time of administration of the investigational product must be documented on the appropriate eCRF.

The unblinded pharmacist must ensure that all documentation regarding investigational product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

All packing slips and other shipment documentation must be retained as well as any investigational product return forms. See the Pharmacy Manual for additional details.

6.8. Rationale for the Dose(s) Selected

In a multiple ascending dose study (PRM151F-12GL), PRM-151 administered IV on Days 1, 3, 8, and 15 to subjects with IPF was well tolerated at doses up to 10 mg/kg. Plasma levels of PRM-151 (C_{max} and AUC) were dose proportional across the range of doses from 1 to 10 mg/kg. Furthermore, PRM-151 had a long half-life of 21 to 44 hours. Evidence of efficacy was seen at the lowest dose level evaluated, 1 mg/kg, with a maximum effect, based on change from Baseline in FVC% predicted and DL_{CO}, seen at the 5 mg/kg dose. Based on these findings, a PRM-151 dose of 10 mg/kg was selected for investigation in the current study. Preclinical dose ranging studies indicate that the effective dose range in humans is expected to be 1-10 mg/kg.

7. STUDY PROCEDURES

Detailed descriptions of subject evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study as described in Section7 and in the Schedule of Events (Appendix A).

All data collected are to be recorded on the appropriate eCRF page.

The Investigator at the clinical trial site is responsible for maintaining a record of all subjects pre-screened, screened, and enrolled into the study.

All subjects must provide written informed consent before the performance of any study procedures.

7.1. Informed Consent

Prior to conducting any study-related procedures, written informed consent must be obtained from the subject or the subject's legally authorized representative.

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject by the Investigator or designee in accordance with the guidelines described in Section8.4.2. Documentation and filing of informed consent documents should be completed according to Section 9.6.

7.2. Study Entrance Criteria

At Screening, each subject will be reviewed for eligibility against the study entrance criteria. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented.

7.3. Demographics

Subject demographic information including gender, age, date of birth, race, ethnicity and number of years since diagnosis of IPF will be collected prior to the subject receiving the first dose of PRM-151.

7.4. Past Medical History

Medical history will be recorded in the eCRF. Any relevant and/or significant previous or existing medical condition(s) that occurred within 5 years prior to time of informed consent) should be reported as medical history. Prior and current therapies for IPF will be recorded in the eCRF.

7.5. Height and Weight

Height will be recorded at Screening for all subjects. Weight will be recorded at Screening; Baseline (dosing days 1, 3, 5); Weeks 4, 8, 12, 16, 20 and 24 for all subjects.

7.6. Laboratory Variables

Clinical laboratory tests will be performed by the local clinical laboratory facility.

7.6.1. Hematology and Clinical Chemistries

Blood samples for hematology, clinical chemistries and coagulation are to be collected during Screening; Baseline; Weeks 4, 8, 12, 16, 20 and 24; and at Week 28.
The following laboratory parameters are to be measured:

Hematology; Hematocrit, Platelet count, White blood cell (WBC) count, Red blood cell (RBC) count, Hemoglobin, Lymphocytes, Eosinophils, Neutrophils, Monocytes, Basophils.

Serum Chemistries and Liver Function Tests; Chloride, Potassium, Blood urea nitrogen (BUN), Creatinine, Albumin, Aspartate aminotransferase (AST), Total bilirubin, Sodium, Bicarbonate (CO_2), Calcium, Glucose, Alkaline phosphatase (ALK), Alanine aminotransferase (ALT), Total protein.

Coagulation Tests: Prothrombin time (PT), Partial Thromboplastin time (PTT), International Normalized Ratio (INR)

7.6.2. Pregnancy Testing

Serum pregnancy testing is required for female subjects of child-bearing potential. A female of childbearing potential is a sexually mature woman who has not undergone a hysterectomy, bilateral oophorectomy, or tubal ligation or is not naturally postmenopausal (i.e., has had menses at any time within the previous 24 months).

Pregnancy testing is to be performed during Screening. Pregnancy testing should be repeated during treatment any time pregnancy is suspected.

During Screening, results must be reviewed and confirmed to be negative for the subject to be eligible for enrollment in the study. If positive pregnancy test results are obtained after the start of study drug treatment, study drug is to be unblinded and discontinued. Pregnancies are to be reported and followed as described above.

7.7. Physical Examination

A complete physical examination is to be performed during Screening and an abbreviated physical exam thereafter. The complete physical examination is to include measurement of height during Screening. Weight is to be measured as part of the complete physical examination during Screening as throughout the study for use in weight based dose calculations.

Complete physical examinations also will include a review of the following body systems:

- General appearance.
- Head, eyes, ears, nose, and throat.

- Respiratory.
- Cardiovascular.
- Abdomen.
- Neurologic.
- Extremities.
- Dermatologic.

Full physical examinations are to be performed at screening; Abbreviated physical exams are to be performed thereafter.

The findings of each examination are to be documented in the eCRF.

If an abnormality noted on physical examination is considered by the Investigator to be clinically significant, then the abnormality is to be recorded as part of the subject's medical history if occurring prior to start of dosing and as an AE occurring if after the start of study drug administration at Week 0, where the finding represents a change from Baseline.

7.8. Vital Signs

Vital signs, including measurement of systolic and diastolic blood pressure, pulse, heart rate, respiration rate, and O_2 saturation, are to be measured in the sitting position during Screening; Baseline (Week 0 Days 1,3, and 5); Weeks 4, 8, 12, 16, 20, 24 and 28.

If a vital sign abnormality is considered by the Investigator to be clinically significant, then the abnormality is to be recorded as part of the subject's medical history if occurring prior to start of dosing and as an AE occurring if after the start of study drug administration at Week 0, where the finding represents a change from Baseline.

7.9. Concurrent Medications

All prescription and non-prescription medications including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 4 weeks prior to the first dose of PRM-151 through the last study visit must be recorded in the eCRF. If on pirfenidone, subject must have been on a stable dose of pirfenidone for at least 3 months without increase in FVC% predicted on two consecutive PFTs, including screening PFTs.

7.9.1. **Prohibited Concurrent Medications**

The following medications are prohibited during the study:

- All investigational therapies other than PRM-151for any indication, including therapies that are approved in other indications that are being investigated in IPF, are prohibited within 4 weeks before Screening and during study participation.
- Immuno-suppressants (e.g., methotrexate, cyclosporine, azathioprine, everolimus).
- Inhaled or systemic corticosteroids. (Low dose [≤10 mg daily] corticosteroids are permissible, provided the dose has been stable for 30 days prior to Baseline.)

- Bronchodilators:
  - Short-acting bronchodilator use within 12 hours of pulmonary function, DLco, and 6MWT assessments.
  - Long acting bronchodilators are disallowed the day of and within 24 hours of pulmonary function, DLco, and 6MWT assessments.
  - The use of inhaled bronchodilator agents at times outside these windows is permissible.

7.10. Efficacy Measurements

On all dosing days, dosing will occur after all safety and efficacy assessments scheduled for that visit are complete.

7.10.1. Pulmonary Function Tests

Spirometry will be measured according to ATS guidelines(Miller, Crapo et al. 2005a), (Appendix B) at Screening, Baseline; Weeks 4, 8, 12, 16, 20, 24, and at the Week 28 visit.

DL_{CO} is to be measured using the single-breath technique according to ATS/ERS guidelines (MacIntyre, Crapo et al. 2005)(Appendix C) at Screening, Baseline and at Week 28 visit. Diffusion capacity should be done on the same day as HRCT.

Lung volumes (TLC and FRC) using Helium dilution method according to ATS guidelines (Wanger, Clausen et al. 2005) will be performed at Screening, Baseline and Week 28.

PFTs will be reviewed centrally by reviewers blinded to treatment group and time point.

7.10.2. Six-minute Walk Test

Exercise tolerance will be evaluate during the 6MWT according to ATS guidelines (ATS 2002) (Appendix D)during Screening, Baseline, Weeks 4, 8, 12, 16, 20, 24, and at the Week 28visit. During the open-labeled extension, subjects will have 6MWT measured every twelve weeks.

7.10.3. High-resolution Computed Tomography

High-resolution Computed Tomography (HRCT) with spirometry will be performed at the Baseline and Week 28.

Spirometry will be performed to ensure that full inspiration HRCT is at Total Lung Capacity (TLC) and full expiration is at Functional Residual Capacity (FRC).

HRCT is to be performed with the subject in the supine position and at full inspiration. Contiguous CT volumetric acquisition will be obtained according to a specified protocol. HRCT scans will be compared using a standardized reading protocol and software to assess treatment-related changes in lung fibrosis.

7.10.4. Patient Reported Outcomes

Kings Brief Interstitial Lung Disease questionnaire (K-BILD) (Patel, Siegert et al.)(Appendix F) is a disease specific questionnaire validated to look at the health status

of subjects with a variety of forms of interstitial lung disease (ILD). It consists of 15 items. The K-BILD questionnaire will be performed at Screening; Baseline, Weeks 4, 8, 12, 16, 20, 24, and at the Week 28 visit.

Leicester Cough Questionnaire (Birring, Prudon et al. 2003)(Appendix G) a self-completed health related quality of life measure of chronic cough. The LCQ total score ranges from 3 to 21 and from 1 to 7 for physical, psychological and social domains; a higher score indicates a better health-related quality of life. The LCQ questionnaire will be performed at Screening; Baseline, Weeks 4, 8, 12, 16, 20, 24, and 28 visit.

7.10.5. Pentraxin-2 Levels

Blood samples for determination of pentraxin-2 levels are to be collected pre-dose at Baseline (Day 1) Weeks 4, 8,12, 16, 20, 24 and at Week 28 (and every 4 weeks pre-dose during the open label extension).

7.10.6. Anti-Pentraxin 2 antibodies (Anti-Drug Antibodies or ADA)

Blood samples for determination of ADA levels are to be collected pre-dose at Baseline and pre-dose at Weeks 4, 8, 12, 16, 20 and 24 and at Week 28 (and every 4 weeks pre-dose during the open label extension).

7.11. Biomarker Assessments

7.11.1. Baseline Genetic Status

The subject's baseline genetic status for TLR3, L412F polymorphism, and MUC5B promoter polymorphism will be collected at Baseline, if available. If the subject has not previously been tested for these genetic characteristics, a blood sample for this analysis should be drawn at baseline.

7.11.2. Optional Blood Sample Collection for Biomarker Assessment

Optional blood samples to study exploratory serum and cellular biomarkers are to be collected pre-dose at Baseline, Week 28 and at Week 128 of the open label extension.

7.12. Safety Measurements

7.12.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to study drug.

7.12.1.1. Respiratory Decline Events

For the purposes of this study, such "respiratory decline" events are defined as follows:

- Unscheduled visits to a healthcare professional for respiratory status deterioration.
- Urgent care visit for respiratory status deterioration.
- Hospitalization due to a worsening or exacerbation of respiratory symptoms.

All "respiratory decline" events will be further characterized according to the definitions of IPF related disease exacerbation, as defined according to ATS criteria:

- Unexplained worsening of dyspnea over 1 month.
- Worsened or severely impaired gas exchange.
- New radiographic alveolar infiltrates.
- The absence of another reason for the worsening respiratory symptoms, (pulmonary embolism, congestive heart failure, pneumothorax).
- Acute, unexplained decline in O_2saturation over 1 month.

7.12.1.2. Adverse Drug Reaction

A suspected adverse drug reaction (ADR) is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Health Authority safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

7.12.1.3. Unexpected Adverse Event

An unexpected AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.12.1.4. Serious Adverse Event

An AE or suspected ADR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

7.12.2. Adverse Event Assessment

All AEs will be recorded. This includes AEs the subject reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during scheduled study center visits.

Each AE is to be assessed by the Investigator with regard to the following categories.

Serious/Non-Serious

Adverse events that meet the criteria specified above are to be considered serious.

Relationship to Study Drug

Relationship of an AE or SAE to investigational product is to be determined by the Investigator based on the definitions in Table 7-1.

Table 7-1: Adverse Event Relatedness

Relationship to Study Drug	Definition
Not Related	Unrelated to investigational product
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.

Intensity

The Investigator is to determine the intensity of the AE according to the criteria in Table 7-2.

Table 7-2: Adverse Event Grading

Severity	Definition
Grade 1 (Mild):	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate):	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3 (Severe):	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4 (Life-threatening):	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Death):	Death related to AE.

7.12.3. Recording Adverse Events

All AEs, regardless of relationship to study drug, are to be recorded in the Adverse Events eCRF. All AE reports are to contain the following details regarding the AE: a brief description, onset date, duration, intensity, treatment required, relationship to study drug, study drug action taken, outcome, and whether the event is classified as serious.

7.12.4. Reporting Serious Adverse Events

The Investigator must report all SAEs to the Medical Monitor within 24 hours of discovery.

<Name>
<List all SAE reporting information
To be added>

A completed SAE report is to be sent to the Medical Monitor's attention within 24 hours of discovering the event. The initial report should include at least the following information:

- Subject's study number;
- Description and date of the event;
- Criterion for serious; and
- Preliminary assignment of causality to study drug.

The Medical Monitor will contact the Investigator via telephone for follow-up information regarding the SAE, as appropriate.

7.12.4.1. Follow-Up of Adverse Events

The Investigator must continue to follow all SAEs and non-serious AEs considered to be reasonably or possibly related to study drug either until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

7.12.4.2. Reporting Safety Information

The Investigator must promptly report to his or her IRB/EC all unanticipated problems involving risks to subjects. This includes death from any cause and all SAEs reasonably or possibly associated with the use of study drug according to the IRB/EC's procedures.

7.12.4.3. Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis and only in the event of an emergency. 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 subject should continue to participate in the study. All protocol deviations and reasons for such deviations must be noted in the eCRF.

8. STATISTICAL ANALYSES

8.1. Statistical Basis for Sample Size

The primary objective is to demonstrate the efficacy of PRM-151 over placebo on absolute change from baseline to 28 weeks in mean FVC% predicted, hereafter referred to as the primary parameter. The primary parameter will be tested in a model with two types of subjects: subjects on a stable dose of pirfenidone, and subjects not on other treatment for IPF.

The sample size is based on the following assumptions:

- Primary parameter is normally distributed
- Homogeneity of variance, i.e. the standard deviation is the same in both arms, and for both types of subjects.
- PRM-151: placebo equals 2:1.
- Expected value of the primary parameter for subjects on pirfenidone will be -1.5.
- Expected value of the primary parameter for subjects on no other treatment will be -3.
- Expected value of the primary parameter for subjects on PRM-151 will be ≥ 2.
- Standard deviation of the primary parameter is 5
- 75% of subjects will be on a stable dose of pirfenidone
- 25% of subjects will not be on other treatment for IPF
- Significance level (α)=0.05
- Desired power to demonstrate superiority is 80%

Resulting sample size

A sample size of sixty (60) subjects in total (40 PRM-151 and 20 placebo) is enough to demonstrate superiority at P<0.05 with a power of 80%. Stratified randomization will ensure balance of PRM-151: placebo in both types of subjects.

8.2. Statistical and Analytical Plan

8.2.1. Statistical Methods

Continuous variables will be summarized by dose group with descriptive statistics (e.g., number of observations, mean, SD, median, interquartile range, maximum, and minimum). Categorical variables will be tabulated by frequency of subjects per dose group. Efficacy evaluations will be performed using the Full Analysis Set (FAS), defined as all subjects with a Baseline and at least 1 post-Baseline observation for each respective efficacy endpoint. A per-protocol analysis may be carried out based on exclusion of data from the FAS for major protocol violations; details will be included in the Statistical Analysis Plan (SAP). Safety evaluations will be based on the Safety Population, defined as all subjects who receive at least 1 dose of study drug and have a post-Baseline safety

observation. Demographic data will be summarized for all subjects entering the study, and if material differences exist, for the FAS and Safety analysis datasets. (Additional details will be included in the SAP.)

Analyses will be based on observed data only; no data will be imputed.

The comparison of PRM-151 with placebo will be carried out via 2-sided statistical tests at alpha=0.05. The primary parameter will be tested with analysis of covariance (ANCOVA), with change from baseline to 6 months in FVC% predicted as dependent variable (outcome), and treatment, stratum, and treatment by stratum interaction as explanatory variables. Baseline FVC% predicted may be added as a covariate if appropriate.

AEs will be coded by using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number and percent of AEs reported, the number of subjects reporting each AE, and the number of subjects with any AE. A by-subject AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Safety data, including laboratory evaluations and vital signs assessments, will be summarized by time of collection and by treatment group. In addition, change from Baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. The frequency of subjects with abnormal safety laboratory results will be tabulated by treatment.

8.2.1.1. Missing, Unused, and Spurious Data

Analyses will be based on observed data only; no data will be imputed.

8.2.1.2. Subject Disposition

A listing and table of proportions of subjects discontinuing the study for each reason will be provided by treatment / dose group. Details will be included in the Statistical Analysis Plan.

8.2.1.3. Demographic and Baseline Characteristics

Summary statistics will be provided for the demographic and baseline characteristics; details will be in the Statistical Analysis Plan.

8.2.1.4. Subject Adherence

Compliance with study drug will be computed for each subject as proportion of prescribed study drug actually taken. Details will be included in the Statistical Analysis Plan.

8.2.1.5. Concomitant Medications

A listing and table of proportions of subjects taking each concomitant medication will be provided. Details will be included in the Statistical Analysis Plan.

8.2.1.6. Safety Analyses

AEs will be coded by using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number and percent of AEs reported, the number of subjects reporting each AE, and the number of subjects with any AE. A by-subject AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Safety data, including laboratory evaluations and vital signs assessments, will be summarized by time of collection and by treatment group. In addition, change from Baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. The frequency of subjects with abnormal safety laboratory results will be tabulated by treatment.

8.2.1.7. Efficacy Analyses

Efficacy analyses will be carried out as indicated in the Section 8.2.1. Details will be included in the Statistical Analysis Plan.

8.2.1.8. Biomarker Analyses

Analyses of biomarker data will be carried out similarly to the analyses of efficacy.

8.2.1.9. Interim Analyses

There is no interim analysis planned.

8.3. Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the clinical study report.

8.4. Ethical, Legal, and Administrative Considerations

8.4.1. Good Clinical Practice

This study will be conducted according to the protocol and in compliance with GCP, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

The Investigator confirms this by signing the protocol.

8.4.2. Informed Consent

Written informed consent in compliance with 21 Code of Federal Regulations (CFR) § 50 and/or ICH will be obtained from each subject prior to undergoing any protocol-specific tests or procedures that are not part of routine care.

Promedior will provide an informed consent form (ICF) template to the Investigator for use in developing a study center-specific ICF. Prior to submission of the study center-specific ICF to the IRB/EC, the study center-specific ICF must be reviewed and approved

by Promedior. Any changes requested by the IRB/EC must also be approved by Promedior. The final IRB/EC-approved ICF must be provided to Promedior. Revisions to the ICF required during the study must be approved by Promedior, and a copy of the revised ICF provided to Promedior.

Before recruitment and enrollment, each prospective subject (or legal guardian) will be given a full explanation of the study and be allowed to read the ICF. After the Investigator or Sub-investigator is assured that the subject/legal guardian understands the commitments of participating in the study, the subject/legal guardian will be asked to sign and date the ICF.

A copy of the fully signed and dated ICF will be given to the subject. The original will be maintained in the subject's medical record at the study center. All active subjects will sign an updated ICF if revisions are made to the ICF during the course of the study.

8.4.3. Institutional Review Board/Ethics Committee

The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at study centers where IRB/EC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the Investigator.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB/EC as appropriate. The Investigator must submit written approval to Promedior or designee before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/EC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB / EC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/EC with reports of any reportable serious ADRs from any other study conducted with the investigational product. Promedior will provide this information to the Investigator.

Progress reports and notifications of reportable serious ADRs will be provided to the IRB/EC according to local regulations and guidelines.

To ensure compliance with GCP and all applicable regulatory requirements, Promedior or designee may conduct a quality assurance audit.

8.5. Amending the Protocol

Any changes in this research activity, except those to remove an apparent immediate hazard to the subject, must be reviewed and approved by Promedior and the IRB/EC that approved the study. Amendments to the protocol must be submitted in writing to the

Investigator's IRB/EC for approval prior to subjects being enrolled into the amended protocol.

Promedior may make administrative changes (i.e., changes that do not significantly affect subject safety or the study's scope or scientific quality) without any further approvals.

8.6. Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and other study personnel must not disclose such information without prior written approval from Promedior.

Subject confidentiality will be strictly maintained to the extent possible under the law. Subject names must not be disclosed. Subjects will be identified in the eCRFs and other documents submitted to Promedior or its designated representative, by their initials, birth date, and/or assigned subject number. Documents that identify the subject (e.g., the signed ICF) should not to be submitted to Promedior or its designated representative, and must be maintained in confidence by the Investigator.

8.7. Publication Policy

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee comprised of Investigators participating in the study and representatives from Promedior, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor.

9. STUDY MANAGEMENT

9.1. Case Report Forms and Source Documentation

The Sponsor or designee will provide the study centers with eCRFs for each subject.

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. An explanation should be given for all missing data.

The Investigator must electronically sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

9.2. Monitoring

During the course of the study, the CRA will make study center visits to review protocol compliance, compare eCRFs and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements in respect to Good Clinical Practice. eCRFs will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

9.3. Inspections

Regulatory authorities and/or quality assurance personnel from Promedior or its designated representative may wish to carry out such source data checks and/or in-center audit inspections. The investigator assures Promedior of the necessary support at all times. In the event of an audit, the Investigator agrees to allow the Sponsor's representatives and any regulatory agencies access to all study records.

9.4. Financial Disclosure Reporting Obligations

Investigators and Sub-investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its regulatory obligation. Investigators and Sub-investigators must commit to promptly updating the information if any relevant changes occur during the study and for a period of one year after the completion of the study.

9.5. Archiving Study Records

Essential documents should be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

However, these documents should be retained for a longer period if required by the applicable local requirements.

ICH requires that subject identification codes be retained for at least 15 years after the completion or discontinuation of the study.

10. REFERENCES

ATS (2002). "ATS Statement: Guidelines for the Six-Minute Walk Test." AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE **166**: 111-117.

Birring, S. S., B. Prudon, et al. (2003). "Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ)." Thorax **58**(4): 339-343.

De Backer, L. A., W. Vos, et al. "The acute effect of budesonide/formoterol in COPD: a multi-slice computed tomography and lung function study." European Respiratory Journal **40**(2): 298-305.

Fernandez Perez, E. R., C. E. Daniels, et al. (2010). "Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study." Chest **137**(1): 129-37.

Frankel, S. K. and M. I. Schwarz (2009). "Update in idiopathic pulmonary fibrosis." Curr Opin Pulm Med **15**(5): 463-9.

Gillmore, J. D., W. L. Hutchinson, et al. (2004). "Autoimmunity and glomerulonephritis in mice with targeted deletion of the serum amyloid P component gene: SAP deficiency or strain combination?" Immunology **112**(2): 255-264.

Gomer, R. H. and M. L. Lupher, Jr. (2010). "Investigational approaches to therapies for idiopathic pulmonary fibrosis." Expert Opin Investig Drugs **19**(6): 737-45.

Haudek, S. B., Y. Xia, et al. (2006). "Bone marrow-derived fibroblast precursors mediate ischemic cardiomyopathy in mice." Proc Natl Acad Sci U S A **103**(48): 18284-9.

Hawkins, P. N., R. Wootton, et al. (1990). "Metabolic studies of radioiodinated serum amyloid P component in normal subjects and patients with systemic amyloidosis." J Clin Invest **86**(6): 1862-9.

King, T. E., W. Z. Bradford, et al. "A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis." New England Journal of Medicine **370**(22): 2083-2092.

Lupher, M. L., Jr. and W. M. Gallatin (2006). "Regulation of fibrosis by the immune system." Adv Immunol **89**: 245-88.

MacIntyre, N., R. O. Crapo, et al. (2005). "Standardisation of the single-breath determination of carbon monoxide uptake in the lung." European Respiratory Journal **26**(4): 720-735.

Maldonado, F., T. Moua, et al. "Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis." European Respiratory Journal **43**(1): 204-212.

Meltzer, E. B. and P. W. Noble (2008). "Idiopathic pulmonary fibrosis." Orphanet J Rare Dis **3**: 8.

Miller, M. R., R. Crapo, et al. (2005a). "General considerations for lung function testing." Eur Respir J **26**: 153-161.

Miller, M. R., J. Hankinson, et al. (2005b). "Standardisation of spirometry." Eur Respir J **26**: 319-338.

Moeller, A., S. E. Gilpin, et al. (2009). "Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis." Am J Respir Crit Care Med **179**(7): 588-94.

Murray, L. A., Q. Chen, et al. (2011). "TGF-beta driven lung fibrosis is macrophage dependent and blocked by Serum amyloid P." Int J Biochem Cell Biol **43**(1): 154-162.

Nalysnyk, L., J. Cid-Ruzafa, et al. (2012). "Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature." European Respiratory Review **21**(126): 355-361.

Navaratnam, V., K. M. Fleming, et al. (2011). "The rising incidence of idiopathic pulmonary fibrosis in the U.K." Thorax **66**(6): 462-7.

Patel, A. S., R. J. Siegert, et al. "The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire." Thorax. 2012 Sep;67(9):804-10. doi: 10.1136/thoraxjnl-2012-201581. Epub 2012 May 3.

Pilling, D., C. D. Buckley, et al. (2003). "Inhibition of fibrocyte differentiation by serum amyloid P." J Immunol **171**(10): 5537-46.

Pilling, D., D. Roife, et al. (2007). "Reduction of bleomycin-induced pulmonary fibrosis by serum amyloid P." J Immunol **179**(6): 4035-44.

Raghu, G., H. R. Collard, et al. (2011). "An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management." Am J Respir Crit Care Med **183**(6): 788-824.

Raghu, G., D. Weycker, et al. (2006). "Incidence and prevalence of idiopathic pulmonary fibrosis." Am J Respir Crit Care Med **174**(7): 810-6.

Raghunath, S. (2014). "Quantitative Stratification of Diffuse Parenchymal Lung Diseases " PLoS Med **9**(3).

Richeldi, L., R. M. du Bois, et al. "Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis." New England Journal of Medicine **370**(22): 2071-2082.

Verstovsek, S., R. A. Mesa, et al. (2012). "A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis." N Engl J Med **366**(9): 799-807.

Wanger, J., J. L. Clausen, et al. (2005). "Standardisation of the measurement of lung volumes." Eur Respir J **26**(3): 511-522.

Zavaletta, V. A., B. J. Bartholmai, et al. "High Resolution Multidetector CT-Aided Tissue Analysis and Quantification of Lung Fibrosis." Academic Radiology **14**(7): 772-787.

11. APPENDIX A **Schedule of Events**		**Treatment Period**				**Open Label Extension**
		Week 0 (+/-1day)		**W4, W8, W12, W16, W20,W24 (+/- 3days)**	**W28 (+/- 3days)**	**W28-W128 (+/- 3days)**
	Screening ≤ 28days	**Baseline Dosing Day 1**	**Dosing Days 3, 5**	**Dosing Day 1**		
Informed Consent	x					
Demographics	x					
Past Medical History	x					
Inclusion/Exclusion	x	x				
Vital Signs	x	x	x	x	x	x
Physical Exam[1]	x	x		x	x	x
Height (cm)	x					
Weight (kg)	x	x		x		x
Prior/Concomitant Medications	x	x	x	x	x	x
Special list of excluded medications	x	x	x	x	x	x
AE/SAE Assessment		x	x	x	x	x
Efficacy Assessment (must be done in the following order)[2]						
Patient Reported Outcomes; K-BILD & LCQ	x	x		x	x	x
Pulmonary Function Tests (PFTs)	x	x		x	x	x
DL_{CO}[3]	x	x			x	x
FRC &TLC by Helium dilution method[4]	x	x			x	x
HRCT with spirometry[5]		x			x	x
6-minute walk test	x	x		x	x	x
Pregnancy test	x					
Complete Blood Count	x	x		x	x	x
Chemistry, BUN/creatinine	x	x		x	x	x
Coagulation	x	x		x	x	x
Status of baseline genetic characteristics[6]		x				
Anti-pentraxin 2 antibodies (ADA), Pre-dose		x		x	x	x
Pentraxin-2 levels, Pre-dose		x		x		x
Exploratory laboratory assessments (optional)[7]		x			x	x
PRM-151 dosing		x	x	x		x

[1] Full physical exam at screening and an abbreviated physical exam thereafter.

[2] During open-label extension, subjects will have PROs, PFTs and 6MWT every 4 weeks for the first 24 weeks, then every 12 weeks

[3] Diffusion capacity should be done on the same day as HRCT

[4] FRC &TLC by helium dilution method should be done on the same day as HRCT

[5] During open-labeled extension, subjects will have DLco and FRC &TLC by He every 12 weeks and HCRT at 1.5 years (W76) and 2.5 years (W128)

[6] TLR3 L412F polymorphism, MUC5B promoter polymorphism

[7] During open label extension, subjects will have optional exploratory labs at Week 128

12. APPENDIX B PULMONARY FUNCTION TESTS

TABLE 1	Conditions where suboptimal lung function results are likely
Chest or abdominal pain of any cause	
Oral or facial pain exacerbated by a mouthpiece	
Stress incontinence	
Dementia or confusional state	

Position

Testing may be performed either in the sitting or standing position, and the position should be recorded on the report (Miller, Crapo et al. 2005a). Sitting is preferable for safety reasons in order to avoid falling due to syncope. The chair should have arms and be without wheels. If a wheelchair is used, the wheels should be locked. If the standing position is used, a chair can be placed behind the patient/subject, so that they can be quickly and easily moved into a sitting position if they become light-headed during the manoeuvre. Obese subjects, or those with excessive weight at the mid-section, will frequently obtain a deeper inspiration when tested in the standing position. Consequently, forced expiratory volumes and flows may improve with the standing position in these individuals. Normal-weight subjects typically have equivalent values when tested sitting or standing, but, for longitudinal studies, the same test position should be used each time.

Patient details

Age ,height, and weight

The patient's age, height and weight (wearing indoor clothes without shoes) are recorded for using the calculation of reference values. The age should be expressed in years. Height and weight should be expressed with the units in use in the country, corresponding to the ones of the selected reference equation. Body mass index should be calculated as kg2m. The height should be measured without shoes, with the feet together, standing as tall as possible with the eyes level and looking straight ahead, and using an accurate measuring device. For patients with a deformity of the thoracic cage, such as kyphoscoliosis, the arm span from finger tip to finger tip can be used as an estimate of height. Arm span should be measured with the subject standing against a wall with the arms stretched to attain the maximal distance between the tips of the middle fingers.

Therapy

The operator should record the type and dosage of any (inhaled or oral) medication that may alter lung function and when the drugs were last administered.

Subject preparation

Subject should avoid the activities listed in table 2, and these requirements should be given to the patient at the time of making the appointment. On arrival, all of these points should be checked, and any deviations from them recorded.

Subjects should be relaxed as possible before and during the tests.

Patient should be asked to loosen tight fitting clothing. Dentures should normally be left in place; if they are loose, they may interfere with performance and are, therefore, best removed.

Laboratory Details

Ambient temperature, barometric pressure and time of day must be recorded. Temperature is an important variable in most pulmonary function tests and is often measure directly by the instrument. The way in which it is measured and used may vary from instrument to instrument. For example, it may be measured with a simple thermometer or an internal thermistor. Regardless of the method used, it is the responsibility of the laboratory to confirm the accuracy of temperature measurements, and it is the responsibility of the manufacture to describe or provide a clear mechanism for checking the accuracy of instrument temperature measurements. They should also provide instructions on how to respond when acceptable temperature performance cannot be confirmed.

Ideally, when patients return for repeat testing (e.g. at clinic), the equipment and the operator should be the same, and the time of day should be within 2 h of previous test times.

The order for performing lung function tests should take into account the optimum work flow in the laboratory, potential influences of one test on another and the ability of the subject to undertake the test. There should be appropriate delays between tests, as indicated in the subsequent sections of this series of documents. Other orders of testing are acceptable (e.g. static lung volumes, diffusing capacity, dynamic studies, inhalation of bronchodilator agent and then repeat dynamic studies, as taken from table 3), but the order should be kept constant to avoid introducing unanticipated variability to test results.

TABLE 4 Procedures for recording forced vital capacity

Check the spirometer calibration
Explain the test
Prepare the subject
Ask about smoking, recent illness, medication use, *etc.*
Measure weight and height without shoes
Wash hands
Instruct and demonstrate the test to the subject, to include
Correct posture with head slightly elevated
Inhale rapidly and completely
Position of the mouthpiece (open circuit)
Exhale with maximal force
Perform manoeuvre (closed circuit method)
Have subject assume the correct posture
Attach nose clip, place mouthpiece in mouth and close lips around the mouthpiece
Inhale completely and rapidly with a pause of <1 s at TLC
Exhale maximally until no more air can be expelled while maintaining an upright posture
Repeat instructions as necessary, coaching vigorously
Repeat for a minimum of three manoeuvres; no more than eight are usually required
Check test repeatability and perform more manoeuvres as necessary
Perform manoeuvre (open circuit method)
Have subject assume the correct posture
Attach nose clip
Inhale completely and rapidly with a pause of <1 s at TLC
Place mouthpiece in mouth and close lips around the mouthpiece
Exhale maximally until no more air can be expelled while maintaining an upright posture
Repeat instructions as necessary, coaching vigorously
Repeat for a minimum of three manoeuvres; no more than eight are usually required
Check test repeatability and perform more manoeuvres as necessary

TLC: total lung capacity.

(Miller, Hankinson et al. 2005b)

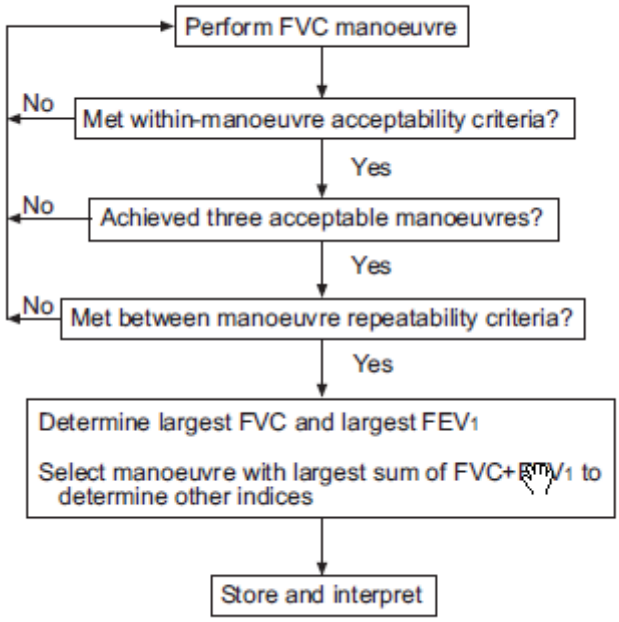
TABLE 5 Summary of within- and between-manoeuvre acceptability criteria

Within-manoeuvre criteria
- Individual spirograms are "acceptable" if
  - They are free from artefacts [3]
    - Cough during the first second of exhalation
    - Glottis closure that influences the measurement
    - Early termination or cut-off
    - Effort that is not maximal throughout
    - Leak
    - Obstructed mouthpiece
  - They have good starts
    - Extrapolated volume <5% of FVC or 0.15 L, whichever is greater
  - They show satisfactory exhalation
    - Duration of ⩾6 s (3 s for children) or a plateau in the volume–time curve or
      - If the subject cannot or should not continue to exhale

Between-manoeuvre criteria
- After three acceptable spirograms have been obtained, apply the following tests
  - The two largest values of FVC must be within 0.150 L of each other
  - The two largest values of FEV_1 must be within 0.150 L of each other
- If both of these criteria are met, the test session may be concluded
- If both of these criteria are not met, continue testing until
  - Both of the criteria are met with analysis of additional acceptable spirograms
    - or
  - A total of eight tests have been performed (optional) or
  - The patient/subject cannot or should not continue
- Save, as a minimum, the three satisfactory manoeuvres

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second.

(Miller, Hankinson et al. 2005b)



(Miller, Hankinson et al. 2005b)

13. APPENDIX C DIFFUSION CAPACITY

Patient conditions for measurement

Factors that affect Vc (e.g. exercise, body position, and Hb affinity for CO, such as alveolar oxygen partial pressure (PA,O2), and carboxyhaemoglobin (COHb)) should be standardized (MacIntyre, Crapo et al. 2005). If clinically acceptable, the subject should not breathe supplemental oxygen for 10 min prior to a standard test. When using exercise or the supine position to assess the ‘‘recruitability’’ of DLco [15, 25–28], the level of exercise and/or the duration of the supine position should be noted.

Before beginning the test, the manoeuvres should be demonstrated and the subject carefully instructed. The subject should be seated comfortably throughout the test procedure. The test should be performed at a stable comfortable temperature within manufacturer’s equipment specifications.

Inspiratory manoeuvre

Once the mouthpiece and nose clip are in place, tidal breathing should be carried out for a sufficient time to assure that the subject is comfortable with the mouthpiece. Deep inspirations should be avoided during this period as they can increase subsequent CO uptake [61]. The DLco manoeuvre begins with unforced exhalation to residual volume (RV). In obstructive lung disease, where exhalation to RV may require a prolonged period, a reasonable recommendation is that this portion of the manoeuvre should be limited to 6 s, a time consistent with using the forced expiratory volume in six seconds manoeuvre as a surrogate for VC [49]. At RV, the subject’s mouthpiece is connected to a source of test gas, and the subject inhales rapidly to TLC.

The inspiration should be rapid, since the DLco calculations assume ‘‘instantaneous’’ lung filling. Slower lung filling decreases the amount of time the lung is at full inspiration with a consequent reduction in CO uptake. Although various sample timing techniques address the issue of lung filling and emptying time, it is still reasonable to expect that 85% of VI should be inspired in, 4.0 s. If longer inspiratory times are needed to achieve the 85% VI goal, this should be noted on the test report.

The intrapulmonary pressure during the breath hold should thus be near atmospheric, and this is best accomplished by having the subject voluntarily maintain full inspiration using only the minimal effort necessary. The breath-hold time should be 10+2s, a target easily achieved in the vast majority of subjects.

As with inspiration, the DLco calculation assumes instantaneous lung emptying. Although various sample timing techniques address the fact that emptying is not instantaneous, it is still reasonable to expect that the expiratory manoeuvre should be smooth, unforced, without hesitation or interruption, and total exhalation time should not exceed 4 s (with sample collection time ,3 s). In subjects who require a longer expiratory time to provide an appropriate alveolar gas sample, the expiratory time should be noted in the test report.

During expiration, a volume of gas must be expired and discarded to clear anatomic and mechanical VD before the alveolar sample is collected

Interval between tests

At least 4 min should be allowed between tests to allow an adequate elimination of test gas from the lungs. The subject should remain seated during this interval. In patients with obstructive airway disease, a longer period (e.g. 10 min) should be considered. Several deep inspirations during this period may help to clear test gases more effectively. If continuous monitoring of expired gas concentrations is available, the washout of tracer gas from the previous test may be confirmed by observing end-tidal gas concentrations before beginning the next test

TABLE 6 Acceptable test criteria for diffusing capacity of the lung for carbon monoxide

Use of proper quality-controlled equipment
V_I of >85% of largest VC in <4 s[#]
A stable calculated breath hold for 10±2 s. There should be no evidence of leaks, or Valsalva or Mueller manoeuvres
Expiration in <4 s (and sample collection time <3 s)[#], with appropriate clearance of V_D and proper sampling/analysis of alveolar gas

V_I: inspired volume; VC: vital capacity; V_D: dead space. [#]: tests outside these timing limits might still have clinical utility, but these deviations from standard acceptability criteria should be noted and possible impact/correction factors considered.

14. APPENDIX D SIX-MINUTE WALK TEST

TECHNICAL ASPECTS OF THE 6MWT
(ATS 2002)

Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.

3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.
4. Pulseoximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable. The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The SpO2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO2. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulseoximeters have considerable motion artifact that prevents accurate readings during the walk.
5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (see APPENDIX E for the Borg scale and instructions).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

   > "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.
   >
   > You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."
   >
   > Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.
   >
   > "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.
   >
   > Start now or whenever you are ready."

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark

the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stop- watch at a race. After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go." When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go." When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done." When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only2 minutes left." When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping pre- maturely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

10. Post-test: Record the post walk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

APPENDIX WORKSHEET

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _____ _____ _____

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____meters

Weight: _____lbs, _____kg Blood pressure: _____/ _____ Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____L/min, type _____

	Baseline	End of Test
Time	___:___	___:___
Heart Rate	_____	_____
Dyspnea	____	____(Borg scale)
Fatigue	____	____(Borg scale)
SpO_2	____%	____%

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ____(X60 meters) + final partial lap: _____meters =

Total distance walked in 6 minutes: _____meters

Predicted distance: _____meters Percent predicted: _____%

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

15. APPENDIX E

Borg Scale for Rating Dyspnea and Overall Fatigue (ATS 2002)

Score	Definition
0	Nothing at all
0.1	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	10 Very, very severe (maximal)

16. APPENDIX F THE KING'S BRIEF INTERSTITIAL LUNG DISEASE QUESTIONNAIRE (K-BILD)

(Patel, Siegert et al.)

The King's Brief Interstitial Lung Disease Questionnaire (K-BILD)©2011

This questionnaire is designed to assess the impact of your lung disease on various aspects of your life. Please circle the response that best applies to you for each question

1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill.						
1. Every time	2. Most times	3. Several Times	4. Some times	5. Occasionally	6. Rarely	7. Never
2. In the last 2 weeks, because of my lung condition, my chest has felt tight.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
3. In the last 2 weeks have you worried about the seriousness of your lung complaint?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
4. In the last 2 weeks have you avoided doing things that make you breathless?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
5. In the last 2 weeks have you felt in control of your lung condition?						
1. None of the time	2. Hardly any of the time	3. A little of the time	4. Some of the time	5. A good bit of the time	6. Most of the time	7. All of the time
6. In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
8. In the last 2 weeks, my lung condition has made me feel anxious.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
10. In the last 2 weeks, how much of the time have you felt your lung disease is getting worse?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
12. In the last 2 weeks have you expected your lung complaint to get worse?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
14. In the last 2 weeks, has your lung condition made you think more about the end of your life?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
15. Are you financially worse off because of your lung condition?						
1. A significant amount	2. A large amount	3. A considerable amount	4.A reasonable amount	5. A small amount	6. Hardly at all	7. Not at all

17. APPENDIX G COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

18. APPENDIX H LEICESTER COUGH QUESTIONNAIRE (LCQ)

(Birring, Prudon et al. 2003)

For Clinic Use Only	
Total:	**/133**

Leicester Cough Questionnaire (LCQ)

Circle the word that matches how serious you feel your cough problem is **overall**:

No Problem Mild Problem Moderate Problem Severe

Circle the word that matches how serious you feel your cough problem is **today**:

No Problem Mild Problem Moderate Problem Severe

Instructions: These questions are designed to assess the impact of your cough on various aspects of your life. Read each question carefully and answer by checking the response that best applies to you in the past **TWO WEEKS**.

		All the time	Most of the time	A good bit of time	Some of the time	A little of the time	Hardly any of the time	None of the time
1	Have you had chest or stomach pains as a result of your cough?	1	2	3	4	5	6	7
2	Have you been bothered by phlegm production when you cough?	1	2	3	4	5	6	7
3	Have you been tired because of your cough?	1	2	3	4	5	6	7
4	Have you felt in control of your cough?	7	6	5	4	3	2	1
5	Have you felt embarrassed by your coughing?	1	2	3	4	5	6	7
6	My cough has made me feel anxious.	1	2	3	4	5	6	7
7	My cough has interfered with my job, or other daily tasks.	1	2	3	4	5	6	7
8	I felt that my cough interfered with the overall enjoyment of my life.	1	2	3	4	5	6	7
9	Exposure to paints or fumes has made me cough.	1	2	3	4	5	6	7
10	Has your cough disturbed your sleep?	1	2	3	4	5	6	7
11	How many times a day have you had coughing bouts?	1	2	3	4	5	6	7
12	My cough has made me feel frustrated.	1	2	3	4	5	6	7
13	My cough has made me feel fed up.	1	2	3	4	5	6	7
14	Have you suffered from a hoarse voice as a result of your cough?	1	2	3	4	5	6	7
15	Have you had a lot of energy?	7	6	5	4	3	2	1
16	Have you worried that your cough may indicate serious illness?	1	2	3	4	5	6	7
17	Have you been concerned that other people think something is wrong with you, because of your cough?	1	2	3	4	5	6	7
18	My cough has interrupted conversations or telephone calls.	1	2	3	4	5	6	7
19	I feel that my cough has annoyed my partner, family or friends.	1	2	3	4	5	6	7

For clinician use only:
(a) Physical: 1,2,3,9,10,11,14,15 (b) Psychological: 4,5,6,12,13,16,17 (c) Social: 7,8,18,19 Domain scores: total score from items in domain/number of items in domain (range 1-7). Total scores: addition of domain scores (range 3-21).

Clinical Trial Protocol: Study PRM-151-202

Study Title:	A Phase 2 Trial to Evaluate the Efficacy of PRM-151 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Study Number:	PRM-151-202
Study Phase:	2
Product Name:	PRM-151
IND Number:	110,774
EUDRACT Number:	2014-004782-24
Indication:	Idiopathic Pulmonary Fibrosis (IPF)

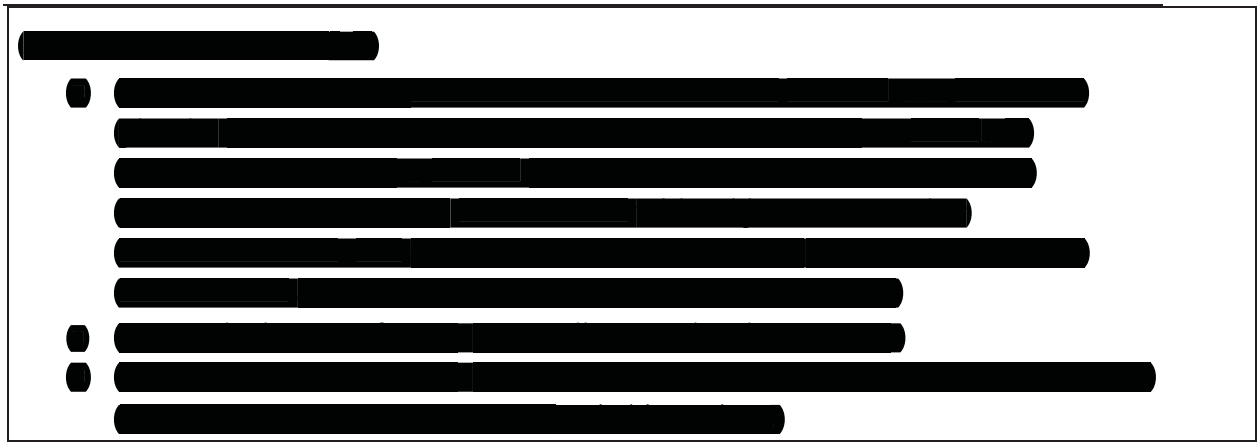
Sponsor: Promedior, Inc
101 Hartwell Ave.
Lexington, MA 02421
Tel: 1-781-538-4200
Fax: 1-781-538-4300

Sponsor Contact: [redacted]
Medical Director: [redacted]
Medical Monitor: [redacted]

	Date
Original Protocol:	Version 1.0 11 November 2014
Amendment # 1:	Version 2.0 26 February 2015
Amendment # 2:	Version 3.0 11 March 2015
Amendment # 3:	Version 4.0 3 February 2016

SYNOPSIS

Sponsor: Promedior, Inc
Name of Finished Product: Recombinant human Pentraxin-2; PRM-151
Study Title: A Phase 2 Trial to Evaluate the Efficacy of PRM-151 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Study Number: PRM-151-202
Study Phase: Phase 2
Investigational Product; Dose; and Mode of Administration: PRM-151 10 mg/kg every 4 weeks via intravenous infusion over 60 minutes. On all dosing days, dosing will occur ***after*** all safety and efficacy assessments scheduled for that visit are completed.
Comparator Dose; and Mode of Administration: Placebo will be administered via IV infusion over 60 minutes.
Primary Objective: • Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF.
Secondary Objective(s): • Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on high- resolution CT (HRCT) imaging analysis, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF. • Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone or nintedanib and separately in subjects not on other treatments for IPF. • Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on HRCT imaging analysis, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF. • Assess the tolerability and safety of PRM-151 in subjects with IPF through Week 28 • Assess the ability of PRM-151 to reduce disease-related events associated with mortality. • Determine the effect size of PRM-151 relative to placebo on pulmonary function in addition to mean change in FVC% predicted. • Determine the effect size of PRM-151 relative to placebo on 6-minute walk distance. • Assess the effect size of PRM-151 relative to placebo on Hb-corrected DLCO.



Study Endpoints:
Primary:

- The primary endpoint is the mean change in FVC % predicted from Baseline to Week 28.

Secondary:

- **Structural Imaging:**
  - Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA) including ground glass density, reticular changes, and honeycombing, using quantitative imaging software.
  - Mean change from Baseline to Week 28 in volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of normal lung (non-ILA), including normal and mild low attenuation areas, using quantitative imaging software.
  - Correlation between mean change from Baseline to Week 28 in FVC % predicted and mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA), including ground glass density, reticular changes, and honeycombing by quantitative imaging software.
- **Safety**: Tolerability/safety will be assessed over the 28-week study period by the following parameters:
  - Incidence of AEs.
  - Incidence of serious adverse events (SAEs).
  - Incidence of respiratory AEs and SAEs.
  - Proportion of subjects discontinuing study drug due to AEs.
  - Change from Baseline in hematology and serum chemistries.
  - All-cause mortality.
  - Mortality due to respiratory deterioration.
- **Disease related events associated with mortality**: The number of "respiratory decline" events over the 28-week study period as defined below:
  - Unscheduled visits to a healthcare professional for respiratory status deterioration.
  - Urgent care visits for respiratory status deterioration.
  - Hospitalization due to a worsening or exacerbation of respiratory symptoms.

  All "respiratory decline" events will be further characterized according to the definitions of IPF-related acute exacerbation, as proposed by an expert committee sponsored by the IPF Clinical Research Network and the National Heart Lung and Blood Institute (NHLBI) (Collard, Moore et al. 2007) and applied by (Collard, Yow et al. 2013)
  - Acute onset of symptoms (< 30 days in duration)
  - New radiographic abnormalities (bilateral ground glass or consolidation on HRCT with no pneumothorax or pleural effusion)
  - The absence of an identified infectious etiology by routine clinical practice

- Exclusion of alternative causes by routine clinical practice, including:
  a. Left heart failure
  b. Pulmonary embolism
  c. Identifiable cause of acute lung injury

- **Pulmonary Function Tests**
  - Proportion (%) of subjects with a decline in FVC% predicted of ≥ 5% and ≥ 10% from Baseline to Week 28.
  - Proportion (%) of subjects with a decline in FVC in ml of ≥ 100 ml and ≥ 200 ml from Baseline to Week 28.
  - Proportion of subjects with an increase in FVC % predicted of ≥ 5% and ≥ 10% from Baseline to Week 28.
  - Proportion of subjects with an increase in FVC in ml of ≥100 ml and ≥ 200 ml from Baseline to Week 28.
  - Proportion of subjects with stable disease by FVC %, defined as a change in FVC % predicted of <5% from Baseline to Week 28.
  - Proportion of subjects with stable disease by FVC in ml, defined as a change in FVC of < 100ml from Baseline to Week 28.
  - Mean change from Baseline to Week 28 in % predicted Hb-corrected diffusion capacity of carbon monoxide (DLCO).
  - Change in 6-minute walk distance, in meters, from Baseline to Week 28.

Exploratory:

- **Other Weeks**
  - Examine the change from Baseline at Weeks 4, 8, 12, 16, 20, 24 and 28 for the FVC % predicted, FVC in ml, and 6MWT distance
- **Structural Imaging**
  - Transitions from Baseline to Week 28 between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and mild, moderate, and severe low attenuation areas) by quantitative imaging software.
  - Correlation of transitions between categories of lung features by quantitative imaging and changes in FVC% predicted.
  - Correlation of transitions between categories of lung features by quantitative imaging and changes in Hb-corrected DLCO.
  - Impact of inspiratory effort on results of HRCT quantitative imaging.
- **Patient Reported Outcomes**
  - Change in Patient Reported Outcomes as measured by King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and Leicester Cough Questionnaire (LCQ) from Baseline to Week 28.
- [redacted]

Study Design:
This study is a Phase 2, randomized, double-blind, placebo controlled, pilot study designed to evaluate the efficacy and safety of PRM-151 administered through Week 24 to subjects with

IPF. Subjects meeting the eligibility criteria for the study will be randomized with a 2:1 ratio to PRM-151 at a dose of 10 mg/kg every 4 weeks or placebo. The randomization will be stratified according to other treatments for IPF (subjects receiving pirfenidone or nintedanib and subjects with no other treatment for IPF, with a minimum of 25% of subjects on no other treatment). Efficacy will be evaluated through pulmonary function tests (PFTs) including spirometry, Hb-corrected Diffusion Capacity (DLco) and Total Lung Capacity by Nitrogen washout method, quantitative imaging analysis of high resolution CT (HRCT), 6-minute walk test (6MWT), and subject reported outcomes (PROs).
Subjects will be evaluated for study eligibility during Screening within 4 weeks before enrollment and Baseline assessments. Subjects who are determined to be eligible, based on Screening assessments, will be enrolled in the study and randomly allocated to treatment with PRM-151 or placebo. Subjects will receive study drug treatment for at least 24 weeks. Approximately 117 subjects will be randomly assigned on a 2:1 basis to treatment with PRM-151 or placebo, as follows:

- PRM-151 10 mg/kg IV infusion over 60 minutes days 1, 3, and 5, then one infusion every 4 weeks
- Placebo IV infusion over 60 minutes on days 1, 3, and 5, then one infusion every 4 weeks

After completion of study treatment through Week 24, all subjects may receive PRM-151 10 mg/kg IV infusion over 60 minutes Days 1, 3, and 5, then once every 4 weeks for an indefinite period of time in an open label study extension. Dosing on Days 1, 3 and 5 will be repeated once every 28 weeks.

Study Duration:
Subjects will receive study drug for a minimum of 24 weeks.
Subjects will participate in the study for an indefinite period of time, including a 4-week screening period, 24-week treatment period, and an open-label treatment extension period,and a 4-week follow up visit.

Study Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Subject is aged 40-80 years.
2. Subject has IPF satisfying the ATS/ERS/JRS/ALAT diagnostic criteria (Raghu, Collard et al. 2011).
   In the absence of a surgical lung biopsy, HRCT must be "consistent with UIP" defined as meeting either criteria A, B, and C, or criteria A and C, or criteria B and C below:
   - **A.** Definite honeycomb lung destruction with basal and peripheral predominance.
   - **B.** Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis, with basal and peripheral predominance.
   - **C.** Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern.
3. If on pirfenidone or nintedanib, subject must have been on a stable dose of pirfenidone or nintedanib for at least 3 months prior to screening without increase in

FVC% predicted on two consecutive PFTs, including screening PFTs. Subjects may not be on both pirfenidone and nintedanib.

4. If not currently receiving pirfenidone or nintedanib, subject must have been off pirfenidone or nintedanib for ≥ 4 weeks before baseline.
5. Subject has a FVC ≥ 50% and ≤ 90% of predicted.
6. Subject has an Hb corrected and/or Hb uncorrected DL_{CO} ≥ 25% and ≤ 90% of predicted.
7. Minimum distance on 6MWT of 150 meters.
8. Subject has a forced expiratory volume in 1 second (FEV_1)/FVC ratio > 0.70.
9. Women of child bearing potential (WCBP), defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if ≤ 55 years or 12 months if > 55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use highly effective methods of birth control throughout the study. Highly effective methods of contraception include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation by oral, intravaginal, or transdermal administration; progestogen-only hormonal contraception associated with inhibition of ovulation by oral, injectable, or implantable administration; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; partner vasectomy, and total abstinence (only if total abstinence is the preferred method and usual lifestyle of the subject). Adequate contraceptive use should be continued until 28 days after the final dose of the study drug.
10. Subject has a life expectancy of at least 9 months
11. Subject, according to the investigator's best judgment, can comply with the requirements of the protocol.
12. Subject and the treating physician considered all medicinal treatment options and / or possibly a lung transplantation prior to considering participation in the study. If the subject is on a lung transplant list, the investigator anticipates the subject will complete the study prior to transplant.
13. Subject has provided written informed consent to participate in the study.

Exclusion Criteria:

1. Subject has emphysema ≥ 50% on HRCT or the extent of emphysema is greater than the extent of fibrosis according to reported results from the most recent HRCT.
2. Subject has a history of cigarette smoking within the previous 3 months.
3. Subject has received investigational therapy for IPF within 4 weeks before baseline.
4. Subject is receiving systemic corticosteroids equivalent to prednisone > 10 mg/day or equivalent within 2 weeks of baseline.
5. Subject received Immuno-suppressants (e.g. azathioprine, cyclophosphamide, or cyclosporine or other immunosuppressants including those used after organ transplant) within 4 weeks of baseline. Subject has a history of a malignancy within the previous 5 years, with the exception of basal cell skin neoplasms. In addition, a malignant diagnosis or condition first occurring prior to 5 years must be considered cured, inactive, and not under current treatment.

6. Subject has any concurrent condition other than IPF that, in the Investigator's opinion, is unstable and/or would impact the likelihood of survival for the study duration or the subject's ability to complete the study as designed, or may influence any of the safety or efficacy assessments included in the study.
7. Subject has baseline resting oxygen saturation of < 89% on room air or supplemental oxygen.
8. Subjects that are unable to refrain from use of the following:
    a) Short acting bronchodilators on the day of and within 12 hours of pulmonary function, DL_{CO}, and 6-minute walk assessments.
    b) Long acting bronchodilators on the day of and within 24 hours of these assessments.
9. Subject has a **known** post-bronchodilator (short-acting beta agonist [SABA] – albuterol or salbutamol) increase in FEV_1 of >10% and in FVC of >7.5%.
10. Female Pregnant and/or lactating subject.

Efficacy Assessments:

Treatment Period: Efficacy related Assessments

Subjects undergo testing on an every 4-week basis after randomization (occurring at Weeks 4, 8, 12, 16, 20, 24 and 28) for efficacy and safety.

During treatment, PFTs, 6MWT, and PROs will be performed on an every 4-week basis. HRCT will be performed on Day 1 as the Baseline assessment and again at the completion of treatment at Week 24. HRCT and PFTs must be done on the same day. PFTs will be reviewed centrally by reviewers blinded to treatment group and time point.

[redacted]

Open Label Post-Study Treatment Extension

After completing 24 weeks of treatment, all subjects will be offered the option to receive PRM-151 in an open-label PRM-151 treatment extension period for an indefinite period of

time. All subjects will receive PRM-151 10 mg/kg IV Days 1, 3, 5 and every 4 weeks in the extension. Dosing on Days 1, 3 and 5 will be repeated once every 24weeks in the extension. PROs, PFTs, and 6MWT will be done every 4 weeks for the first 24 weeks and then every 12 weeks and DLco, FRC & TLC by nitrogen washout method and HRCT will be done at 1.5 years (Week 76) and 2.5 years (Week 128).

Safety Assessments:

Treatment Period: Tolerability/Safety-Related Assessments

Safety will be evaluated from reported adverse events (AEs), scheduled physical examinations, vital signs, and clinical laboratory test results. Adverse events and concomitant medications will be assessed at all study visits. In addition, information regarding hospitalizations, emergency department visits, and unscheduled or urgent care visits to a health care provider due to a deterioration in respiratory status or symptoms will be collected at all study visits.

Statistical Methods:

The primary analysis is planned after last subject completed W28 assessment. Continuous variables will be summarized by dose group with descriptive statistics (e.g., number of observations, number of missing observations, mean, SD, median, interquartile range, maximum, and minimum). Categorical variables will be tabulated by frequency of subjects per dose group, and percentages will be calculated using the number of available observations as the denominator (i.e. excluding missing values). Efficacy evaluations will be performed using the Full Analysis Set (FAS), defined as all subjects with a Baseline and at least 1 post-Baseline observation for the primary efficacy endpoint. A per-protocol analysis will also be carried out on the Per Protocol (PP) set, a subset of the FAS composed of all subjects treated with the IMP, having received at least the planned IMP infusions on days 1, 3, 5, and weeks 4, 8 and 12 and who did not present any major protocol deviations.

The per-protocol set will be used for secondary analyses of the primary efficacy criterion and for the analysis of some selected secondary efficacy criteria. Safety evaluations will be based on the Safety Population, defined as all subjects who receive at least 1 dose of study drug and have a post-Baseline safety observation. Demographic data will be summarized for all subjects entering the study, and if material differences exist, for the FAS and Safety analysis datasets. (Additional details will be included in the SAP.)

This study is randomized with a 2:1 randomization ratio. A central randomization system will be used. The randomization will be stratified according to the subject's baseline treatment status: baseline pirfenidone or baseline nintedanib or no other therapy for IPF at baseline. The randomization system will also ensure that at least 25% of the subjects in the final study population are on no other therapy for IPF at baseline.

The comparison of PRM-151 with placebo will be carried out via 2-sided statistical tests at alpha=0.10. The primary endpoint will be tested with analysis of variance (ANOVA), with change from Baseline to week 28 in FVC% predicted as dependent variable (outcome), and treatment and stratum, as explanatory variables. FVC% predicted will also be analyzed separately for each level of the stratum variable (in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF) using analysis of variance

(ANOVA), with change from Baseline to week 28 in FVC% predicted as dependent variable (outcome), and treatment as the explanatory variable. In case of missing Week 28 assessment of FVC% predicted, the last available observation will be carried forward.

A similar analysis will be done for the secondary and exploratory endpoints, replacing FVC % predicted with the other endpoints as appropriate. Analyses over time will use a three-way ANCOVA with time (nominal study week) as the third factor, including all interactions. The analysis will adjust for correlated errors over time.

For all secondary and exploratory efficacy endpoints, the analyses will be based on observed data only; no data will be imputed.

AEs will be coded by using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number and percent of AEs reported, the number of subjects reporting each AE, and the number of subjects with any AE. A by-subject AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Safety data, including laboratory evaluations and vital signs assessments, will be summarized by time of collection and by treatment group. In addition, change from Baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. The frequency of subjects with abnormal safety laboratory results will be tabulated by treatment.

Sample Size Considerations:
The primary objective is not to formally demonstrate the superiority of PRM-151 over placebo, but to provide a reliable estimate of the size of the effect of PRM-151 on change from baseline to 28 weeks in mean FVC% predicted, hereafter referred to as the primary endpoint. Nevertheless, the sample-size has been calculated to ensure a sufficient power to demonstrate the efficacy of PRM-151 over placebo on the primary endpoint under a set of hypotheses on effect sizes in the two groups and on the variability of the primary endpoint. The primary endpoint will be tested in a model taking into account the stratification variable (two types of subjects: subjects on a stable dose of pirfenidone, and subjects not on other treatment for IPF). The sample size calculation is based on the following assumptions:

- Primary endpoint is normally distributed.
- Homogeneity of variance, i.e. the standard deviation is the same in both arms, and for both types of subjects.
- Randomization ratio PRM-151: placebo equals 2:1.
- Expected value of the primary endpoint for subjects on pirfenidone or nintedanib will be -1.5.
- Expected value of the primary endpoint for subjects on no other treatment will be -3.
- Expected value of the primary endpoint for subjects on PRM-151 will be ≥ 0.75.
- Standard deviation of the primary endpoint is 5.
- 75% of subjects will be on a stable dose of pirfenidone or nintedanib.

- 25% of subjects will not be on other treatment for IPF.
- Significance level (α) = 0.10.
- Desired power to demonstrate superiority is 80%.

A sample size of one hundred and two (102) evaluable subjects in total (68 PRM-151 and 34 placebo) is enough to demonstrate superiority at $p < 0.10$ with a power of 80% under the above assumptions. Assuming a non-evaluability rate of about 15%, 117 subjects in total (78 PRM-151 and 39 placebo) are to be enrolled. Stratified randomization will ensure a balance of PRM-151: placebo in subjects on pirfenidone or nintedanib and not on any other therapy.

Date of Original Protocol: Version 1.0 11 November 2014

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LIST OF ABBREVIATIONS

Abbreviation	Term
6MWD	6-Minute walk distance
6MWT	Six-minute walk test
ADL	Activities of daily living
ADA	Anti-Drug Antibodies/Anti-Pentraxin 2 antibodies
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALAT	Latin American Thoracic Association
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC_{0-24}	Area under the curve from time 0 to 24 hours
$AUC_{0-\infty}$	Area under the curve from time 0 extrapolated to infinity
BAL	Bronchoalveolar lavage
BID	Twice daily
BRT	Bronchodilator reversibility testing
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CTGF	Connective tissue growth factor
DL_{CO}	Diffusion Capacity of Carbon Monoxide
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
ECM	Extracellular matrix
eCRF	Electronic case report form
ERS	European Respiratory Society
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
hPTX-2	Human pentraxin-2
HRCT	High-resolution computed tomography

Abbreviation	Term
hSAP	Human serum amyloid P(synonymous with hPTX-2)
IC	Inspiratory capacity
ICAM-1	Intercellular adhesion molecule-1
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL	Interleukin
ILA	Interstitial Lung Abnormality
ILD	Interstitial Lung Disease
IND	Investigational New Drug Application
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IV	Intravenous
JRS	Japanese Respiratory Society
LAA	Low Attenuatino Areas
LOXL2	Lysyl oxidase-like 2 protein
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
Mreg	Regulatory macrophages
mRNA	Messenger ribonucleic acid
O_2	Oxygen
PDGF	Platelet-derived growth factor
PFT	Pulmonary function test
PK	Pharmacokinetics
pp	Percentage points
PRO	Patient Reported Outcome
PTX-2	Pentraxin-2
q2w	Every 2 weeks
q4w	Every 4 weeks
RBC	Red blood cell
SABA	Short-acting beta agonist
SAE	Serious adverse event
SAP	Serum amyloid protein, also Statistical Analysis Plan
SD	Standard deviation
SD-SOBQ	San Diego-Shortness of Breath Questionnaire
SGRQ	St. George Respiratory Questionnaire

Abbreviation	Term
SP-D	Surfactant protein D
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
TK	Toxicokinetic
TWA	Time-weighted average
UK	United Kingdom
US	United States
VCAM-1	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
WBC	White blood cell

1. INTRODUCTION AND STUDY RATIONALE

1.1. Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a rare, specific form of chronic, fibrosing, interstitial pneumonia limited to the lung. In the United States (US), IPF is estimated to affect up to 135,000 individuals, with approximately 50,000 cases being diagnosed annually (Raghu, Weycker et al. 2006). It is estimated that each year, 40,000 people in the US die due to IPF or complications thereof (Raghu, Weycker et al. 2006), the same as for breast cancer. There is limited information regarding the incidence and prevalence of IPF in the European Union (EU); however, it is estimated that up to 40,000 individuals are affected, with 5,000 cases diagnosed annually in the United Kingdom (UK) alone (Navaratnam, Fleming et al. 2011). IPF incidence and prevalence increase with age and are higher among males (Nalysnyk, Cid-Ruzafa et al. 2012). Overall, it is estimated that worldwide, 5 million individuals may be affected(Meltzer and Noble 2008). Although rare, the incidence of IPF is increasing, likely due to an increasing understanding of the disease and the recent development of uniform diagnostic criteria (Nalysnyk, Cid-Ruzafa et al. 2012)

IPF is a progressive disease with significant morbidity and mortality. The precise initiating injury is unknown, and the clinical course of IPF is variable. The fibrosis that develops in IPF follows a similar path to normal wound healing, but is progressive and without resolution. 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 alveoli. 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.

Ultimately, IPF leads to death, with a median survival after diagnosis of 3 years and a 5-year survival rate of 20% to 40% (Gomer and Lupher 2010). Estimates are that IPF is the primary cause of death for 60% of subjects 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).
No cure currently exists for IPF. There are two approved therapies in the United States and one in Europe. Pirfenidone was approved in the EU on February 28, 2011, for treatment of mild to moderate idiopathic pulmonary fibrosis (IPF), based on a statistically significant reduction in the decline of percent predicted FVC from Baseline at Week 72 (p=0.001) in subjects receiving pirfenidone compared with subjects receiving placebo.

Pirfenidone received approval in the US on October 15, 2014, for treatment of Idiopathic Pulmonary Fibrosis, based on the previous data and a new Phase 3 study, which demonstrated a statistically significant treatment effect of pirfenidone compared to placebo in change in % FVC from baseline to Week 52, with the proportion of subjects declining being lower on pirfenidone than on placebo. Nintedanib was approved in the US on October 15, 2014, for Idiopathic Pulmonary Fibrosis, based on a statistically significant reduction in the annual rate of decline of FVC (in mL) in subjects receiving nintedanib compared to subjects receiving placebo in 3 clinical trials.

As effective treatment options for IPF have been limited until recently, affected subjects also receive supportive therapies and palliative care. As the clinical course of IPF is variable, strategies to treat the disease are individualized, based on the subject's medical history and clinical condition. Such treatments may include long-term oxygen (O_2) therapy; pulmonary rehabilitation; opiates; anti-reflux therapy; and low dose corticosteroids to treat cough. Although such therapies may ameliorate subjects' symptoms and improve comfort, they do not slow the progression of the disease or prolong survival. One exception is lung transplantation, which may be considered for subjects at increased risk of mortality, leads to an improvement in 5-year survival post-transplantation to 50 to 56% (Raghu, Collard et al. 2011).However, transplantation is generally recommended for subjects aged <60 years and, given that IPF is primarily a disease of the elderly with a mean age at diagnosis of 74 years (Fernandez Perez, Daniels et al. 2010), most subjects do not fall into a group for which transplant is a likely option.

1.2. PRM-151

Pentraxin-2 (PTX-2), also called serum amyloid P (SAP), is an endogenous protein that circulates in the bloodstream. 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 on monocytes and promotes their differentiation into regulatory macrophages (Mreg), 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. Both increased fibrocyte numbers in circulation (Moeller, Gilpin et al. 2009) and decreased levels of circulating PTX-2 (Murray, Chen et al. 2011) have been characterized in IPF subjects relative to healthy subjects.

PRM-151 is a recombinantly-expressed version of human pentraxin-2 (hPTX-2). Like the native human protein, PRM-151 is expressed and purified as a non-covalent, homo-pentameric glycoprotein. Each monomer in the pentamer is comprised of 204 amino acids with one N-linked glycosylation site at Asn32 possessing a typical complex biantennary structure. There is one intramolecular disulfide bond between the only 2 cysteine residues in each monomer: Cys36-Cys95. The average molecular weight of the fully glycosylated, sialylated pentamer is 127313 Da.

Preclinical and clinical data exist to support the investigation of PRM-151 in the treatment of fibrotic diseases.

1.2.1. Preclinical Pharmacology

Following the initial *in vitro* discovery by Gomer and Pilling suggesting that PTX-2 may regulate monocyte differentiation into spindle shaped fibrocytes (Pilling, Buckley et al. 2003), they, with others, published several studies on the activity of species-specific serum-derived PTX-2 in preventing fibrosis in models of bleomycin-induced lung fibrosis in rats and mice and also in a model of ischemia reperfusion injury to mouse heart (Pilling, Roife et al. 2007),(Haudek, Xia et al. 2006). Promedior and its collaborators have expanded the animal fibrosis model data using human serum-derived PTX-2 and PRM-151 to demonstrate potent anti-fibrotic activity in models of lung injury, skin injury, kidney injury, liver injury, radiation-induced injury, and a rabbit trabeculectomy model of eye injury.

1.2.2. Nonclinical Metabolism and Pharmacokinetics

The half-life ($t_{1/2}$) of IV-dosed PTX-2/PRM-151 (2-7 mg/kg) has been calculated for multiple species, with the following results: mouse (4-8 hr) < rabbit (7.3 hr) < monkey (6-15 hr) < rat (13-23 hr) < human (30 hr, [human $t_{1/2}$ from Promedior single, ascending dose study, PRM151A-11EU; 10 mg/kg dose in healthy volunteers])(Hawkins, Wootton et al. 1990)

[redacted]

1.2.4. **Clinical Experience in Healthy Subjects and Subjects with IPF and Myelofibrosis (MF)**

PRM-151 administered IV has been investigated in 18 healthy subjects and in 18 subjects with IPF. PRM-151 is being investigated in an ongoing Phase 2 study in subjects with MF in which 27 subjects enrolled, 20 subjects completed 24 weeks of treatment, and 10 subjects have received at least 36 weeks of treatment in a study extension.

In a single ascending dose study (PRM151A-11EU), there were no dose limiting toxicities and no serious adverse events (SAEs) were noted. The most frequent (≥15%) treatment-emergent adverse events (TEAE) for the PRM-151-treated subjects were fatigue (38%) and headache (19%). Overall, the data indicate that single doses of 0.1, 0.25, 0.5, 1, 2, 5, 10, and 20 mg/kg were safe and well tolerated. The $t_{1/2}$ of IV administered PRM-151 was approximately 30 hours. The PK profile of PRM-151 was linear and similar in healthy subjects and subjects with IPF.

In a multiple ascending dose study (PRM151F-12GL), 21 subjects with IPF were enrolled in successive cohorts of 7 subjects each, randomized 5:2 to receive either PRM-151 or placebo. Each cohort was assigned a progressively increasing dose level of PRM-151: 1, 5, or 10 mg/kg administered IV on Days 1, 3, 5, 8 and 15. Subjects in all 3 PRM-151 dose groups demonstrated improvement in FVC% predicted at Day 57 after receiving PRM-151 on Days 1, 3, 5, 8 and 15. Mean change from Baseline in FVC% predicted at Day 57 was + 2.4 (standard deviation [SD] 3.8) for all PRM-151-treated subjects versus -1.5 (SD 3) for placebo-treated subjects (p=0.0524). Furthermore, 6 out of 14 PRM-151 treated subjects experienced a relative increase from Baseline of at least 5% in FVC % predicted. Review of other pulmonary function tests (PTFs) showed an increase from Baseline in forced expiratory volume in 1 second (FEV_1) in all 3 dose groups, whereas a decrease from Baseline was seen in the placebo group; none of the between group differences was statistically significant. Mean PFTs at Baseline and change from Baseline on Day 57 are summarized in Table 1-1.

Table 1-1: Mean (SD) Pulmonary Function Tests at Baseline and Change from Baseline to Day 57: Study PRM-151F-12GL

		PRM-151			
Parameter	**Placebo (N=6)**	**1 mg/kg (N=5)**	**5 mg/kg (N=5)**	**10 mg/kg (N=4)**	**All Doses (N=14)**
FVC (liters)					
Baseline	2.2 (0.64)	3.0 (0.85)	2.8 (0.73)	3.0 (0.71)	2.9 (0.71)
Δ from Baseline	-0.06 (0.116)	0.06 (0.164)	0.06 (0.074)	0.08 (0.210)	0.06 (0.142)
FVC % predicted (%)					
Baseline	63 (16.7)	82 (15.5)	80 (7.8)	73 (14.3)	79 (12.5)
Δ from Baseline	-1.5 (3.3)	2.4 (4.6)	2.8 (3.0)	1.8 (5.3)	2.4 (4.0)
DL_{CO} (%)					
Baseline	35 (8.4)	41 (10.5)	53 (9.8)	46 (7.2)	47 (10.1)
Δ from Baseline	-2.3 (2.1)	0.2 (3.3)	-4.0 (6.8)	-1.5 (3.8)	-1.8 (4.9)
FEV_1 (%)					
Baseline	69 (17.7)	86 (16.8)	87 (11.9)	73 (12.1)	83 (14.3)
Δ from Baseline	-1.7 (4.3)	2.6 (4.3)	2.4 (1.1)	0.3 (3.8)	1.9 (3.2)

Results of the 6-minute walk test (6MWT) showed that on Day 57, the distance walked was decreased from Baseline by a mean of -11 (SD, 51) meters in the placebo group compared with a numerical improvement in each of the 5 mg/kg, 10 mg/kg, and all dose combined groups [+6 (SD, 43), +35 (SD, 45), and +8 (SD, 51) meters, respectively],

although these differences were not statistically significant. No infusion reactions, no dose-limiting toxicity and no serious adverse events were observed. In addition, no antibodies to PRM-151 were measured. In the PRM-151-treated subjects, the most common adverse events recorded during the study were cough (n = 7; 47%), productive cough (n=4; 27%) followed by fatigue (n = 3; 20%) and headache (n = 3; 20%). The incidence of these events was comparable in the placebo group [cough, 33% (n = 2); productive cough, 33% (n = 2); fatigue, 17% (n = 1) and headache, 17% (n = 1)]. Neither the nature nor the frequency of these reported adverse events increased with ascending PRM-151 dose levels. One subject in the 1 mg/kg dose group experienced an episode of moderate hypotension and dizziness just before administration of the third dose of PRM-151. These symptoms were considered possibly related to PRM-151 administration, and resulted in discontinuation of PRM-151 treatment for that specific subject.

In a Phase 2 study in subjects with myelofibrosis treated with PRM-151 either weekly or every 4 weeks, either alone or added to a stable dose of ruxolitinib, data on all 20 subjects who completed 24 weeks of treatment and 10 who have completed at least 36 weeks of treatment as of Sept. 29, 2014 have demonstrated reduction in bone marrow fibrosis in 9 subjects and improvement in anemia and/or thrombocytopenia in 9 subjects, 5 of whom also had bone marrow improvement. Treatment emergent adverse events have been mostly mild (Grade 1 or 2 by the CTCAE criteria) and unrelated to PRM-151. There were 2 instances of infusion reactions (Grade 2); in each case, subsequent treatments were uneventful with diphenhydramine and dexamethasone administered prior to treatment. There were 5 serious adverse events (SAEs) considered possibly related, including 1 death. These included abdominal pain (recovered), sialadenitis (recovered), respiratory syncytial virus (recovered), and gastroenteritis (norovirus documented in entire family) and pneumonia (death). There were two unrelated deaths including pneumonia (subject voluntarily discontinued all medications including antibiotics and subsequently died) and multi-organ failure and cardiac arrest (automatic implantable cardioverter defibrillator failed) after bone marrow biopsy site hematoma in a subject with a pre-existing arrhythmia. In summary, reported adverse events have been consistent with morbidity and mortality expected in this subject population and with adverse events reported in the treatment and placebo arms of ruxolitinib clinical trials (Verstovsek, Mesa et al. 2012).

Based on these encouraging data, Promedior has planned the current study to investigate the effects of PRM-151administered through Week 24 to a population of subjects with IPF.

1.3. Quantitative Imaging

This study incorporates quantitative imaging to assess the degree of change in pulmonary fibrosis. Background information for the technique is provided below:

1.3.1. Imbio Lung Texture Analysis

Imbio Lung Texture Analysis classifies each voxel of lung parenchyma based on morphology, texture and density characteristics. The quantitative results label each region as normal parenchyma, interstitial lung abnormality (ILA: with ground glass opacity, reticular densities, and honeycombing texture types) and Low Attenuation Areas (LAA; with mild, moderate, and severe types). It quantifies these characteristics by total volume (cm^3) or % total lung volume. Requirements for optimal use of Imbio Lung Texture Analysis software include inspiratory non-contrast enhanced HRCT (images obtained at TLC), volumetric scans with slice thickness ≤ 5mm (ideally less than 2mm), and CT data that has not been modified by edge enhancement filters as part of the reconstruction process. Previous studies have shown that quantification of lung parenchyma by Imbio Lung Texture Analysis is comparable to but more reproducible than radiologist assessment (Zavaletta, Bartholmai et al.), that these parameters correlate with known markers of disease severity such as FVC%, DLCO, 6MWT[2] and GOLD classification (Raghunath 2014) and that changes in ILA features over time are predictive of mortality in UIP (Maldonado, Moua et al.). The Lung Texture Analysis software was previously utilized for quantitative evaluation of HRCT data in greater than 4000 ILD and COPD subjects within the NHLBI/NIH-funded Lung Tissue Research Consortium effort. This technique was used in a retrospective analysis of PRM-151 data as described below and will be used prospectively in this study as a secondary endpoint.

1.3.2. Retrospective Quantitative Imaging Analysis of PRM-151 Data

Imbio Lung Texture Analysis was applied retrospectively to HRCT obtained at screening and Day 57 in Study PRM151f-12GL. Limitations of retrospective analysis included, the fact that the datasets contained reconstructed images of variable slice thickness, reconstruction kernel and temporal correlation with the physiologic tests were available. In particular, the slice thicknesses for some CT scans were ≥ 5 mm for some subjects and volumetric HRCT was not available at both time points for any of the subjects. In addition, validation of the inspiratory volume was not prospectively controlled, with full inspiration of the subjects during the scan assumed but not specifically coached by the performing technologist or measured by spirometry. Lung Texture Analysis results were reported as change from screening to Day 57 in % total lung volume occupied by any of the ILA texture types (ground glass, reticular or honeycombing) and non-ILA (normal parenchyma or mild LAA). Areas of moderate or severe LAA that are characteristic of emphysema were excluded from the analysis. Quantitative imaging data was analyzed in 16 subjects who had ≤ 36 days between screening CT and Day 1 PFTs. There was a strong negative correlation between baseline FVC % predicted and percent of lung volume identified as ILA by Imbio Lung Texture Analysis software. Non-ILA lung decreased in all placebo subjects and was stable or increased in 5 PRM-151 treated subjects, all of whom had stable or increased FVC % predicted. There was no clear correlation between the magnitude of change in FVC% predicted and %Non-ILA, possibly due the limitations inherent to retrospective analysis of the HRCT data. The analysis was confounded in 4 subjects by apparent poor inspiratory effort and resultant

atelectasis and increase in overall lung density for the HRCT series that should have been performed at TLC on the Day 57.

1.4. Rationale for Current Study

IPF is a progressive disease that leads to significant morbidity and mortality, with a median survival after diagnosis of 3 years and a 5-year survival rate of 20 to 40% (Gomer and Lupher 2010). Despite the two recently approved therapies, no therapies have yet been developed for IPF that meaningfully reverse the progressive lung fibrosis that is the basic pathologic feature of the disease and no therapies have reproducibly demonstrated an improvement in lung function. IPF remains a progressive disease with no cure other than lung transplant in selected subjects. Thus, there is still a significant unmet medical need for subjects with IPF, particularly those with severe disease (Nalysnyk, Cid-Ruzafa et al. 2012).

As summarized previously, encouraging efficacy data were obtained in a Phase 1 study of PRM-151 in a relatively small number of subjects with IPF (n=15) who received PRM-151 administered via 30-minute IV infusion at doses of 1, 5, and 10 mg/kg on Days 1, 3, 5, 8, and 15, with all 3 groups demonstrating improvement in FVC % predicted at Day 57. Furthermore, 6 out of 14 PRM-151 treated subjects experienced a relative improvement of at least 5% from Baseline in FVC % predicted. These results seen at 8 weeks post-Baseline after 5 PRM-151 doses administered over 2 weeks are encouraging, particularly considering that the best result with pirfenidone and nintedanib is a reduction in the rate of decline rather than improvement in FVC (King, Bradford et al.; Richeldi, du Bois et al.). Improvements from Baseline were also observed in FVC measured in milliliters and in 6MWT distance for PRM-151-treated subjects. Review of safety data from this study demonstrated that PRM-151at doses up to 10 mg/kg were safe and well tolerated in subjects with IPF. No SAEs were observed over 57 days, and similar types and number of TEAEs were reported in both PRM-151- and placebo-treated subjects.

Based on these encouraging data in a small cohort of subjects with IPF, Promedior has planned to investigate the effects of PRM-151 in the proposed study involving a larger population of subjects with this condition.

1.5. Risk/Benefit Assessment

PRM-151, a recombinant form of an endogenous human protein, has been well tolerated in preclinical toxicology studies and Phase 1 and 2 clinical studies, and has shown an early trend towards efficacy in subjects with IPF. Based on encouraging Phase 1 data in subjects with IPF, PRM-151 has the potential to be a safe, disease modifying treatment for a broad spectrum of fibrotic diseases, including IPF.

PRM-151 represents the recombinant version of an endogenous human serum protein, and as such was predicted to have a very favorable safety index. This prediction has been confirmed in multiple preclinical and clinical studies to date. Two Phase 1 studies of

PRM-151 administered IV to normal volunteers and IPF subjects have been completed, with no SAEs reported and no other safety signals seen. The single ascending dose study (PRM151A-11EU) tested dose levels as high as 20 mg/kg. The multiple ascending dose study (PRM151F-12GL) demonstrated that PRM-151 administered by 30-minute IV infusion on Days 1, 3, 5, 8 and 15 at up to 10 mg/kg was safe and well tolerated in subjects with IPF, with no SAEs noted in 57 days; similar types and number of TEAEs were reported in both PRM-151 and placebo treated subjects. Safety data from 27 subjects with MF, including 24 weeks of safety data in 20 subjects and an additional 12 weeks of safety data in 10, confirms the excellent safety profile of PRM-151 to date. Most adverse events have been Grade 1 or 2 and unrelated to PRM-151, and 5 possibly related SAEs, including one death, have been reported in a group of older subjects (median age 67 years) with a serious, life threatening disease.

Risks associated with PRM-151 are inherent in its being the recombinant form of a naturally occurring human protein, and consist of potential development of anti-drug antibodies and infusion reactions. PRM-151 has an endogenous counterpart, and, therefore, anti-drug antibodies could develop that could potentially affect the efficacy of PRM-151 treatments in addition to having the potential to cross-react with endogenous hPTX-2. Anti-drug antibodies were detected in 3 subjects in the MF trial, with no apparent impact on pharmacokinetics, safety, or efficacy. Two subjects had mild infusion reactions which were easily managed and prevented in the one subject that was rechallenged; anti-drug antibody was detected in one of them.

PRM-151 is not a general immunosuppressant, and treatment with PRM-151 is not expected to increase rates of infection or adversely affect wound healing.

As with any protein therapeutic, the potential for reactions exists and safety procedures will be implemented including careful monitoring of subjects during infusions and of infusion sites. Appropriate personnel, medication, and other requirements for the treatment of potential infusion reactions will be required by the protocol.

PRM-151 is an investigational agent. Subjects are not anticipated to derive direct benefit from participation in studies; the potential benefits of PRM-151 as a therapy for IPF remain to be proven in clinical efficacy studies.

The CT scans performed for this study will involve the delivery of small amounts of radiation to the subject. The dose of radiation expected for the chest HRCT in this protocol has not been found to harm most healthy adults. 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 reasonable achievable" (ALARA) to obtain the quality of images necessary for imaging of lung abnormalities and quantification by Lung Texture 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 (NRC) has adopted a risk value for an occupational dose of 1 rem (0.01 Sieverts) Total Effective Dose Equivalent (TEDE) of approximately 1 chance in 2,500 of fatal cancer per rem of TEDE received. For this protocol, the dose will vary, depending on the specific CT scanner technology available at each site, but the volumetric CT dose index is estimated to be less than 10milliGrey with effective dose for a standard subject of less than 3 milliSieverts (0.003 Sieverts) per scan. Dose will be adjusted appropriately to assure consistent image quality, based on subject size. No populations at potentially higher risk for radiation exposure such as young children or pregnant women will be involved in the study.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective of this study is:

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

2.2. Secondary Objectives

The secondary objectives of this study are:

- Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on high- resolution CT (HRCT) imaging analysis, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF.
- Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on HRCT imaging analysis, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- Assess the tolerability and safety of PRM-151 in subjects with IPF through Week 28.
- Assess the ability of PRM-151 to reduce disease-related events associated with mortality
- Determine the effect size of PRM-151 relative to placebo on pulmonary function in addition to mean change in FVC% predicted
- Determine the effect size of PRM-151 relative to placebo on 6-minute walk distance
- Determine the effect size of PRM-151 relative to placebo on Hb-corrected DLCO.

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- Evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, 24 and 28 in FVC % predicted and 6-minute walking distance, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF and separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- To assess the impact of PRM-151 on disease related symptoms.
- Assess the impact of PRM-151, disease pathogenesis and disease progression on exploratory serum, cellular and genetic biomarkers

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint for the study is:

- Mean change in FVC % predicted from Baseline to Week 28.

3.2. Secondary Endpoints

The secondary endpoints for the study are:

1. **Structural Imaging**:
    - Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA), including ground glass density, reticular changes, and honeycombing, using quantitative imaging software.
    - Mean change from Baseline to Week 28 in volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of normal lung (non-ILA), including normal and mild low attenuation areas, using quantitative imaging software.
    - Correlation between mean change from Baseline to Week 28 in FVC % predicted and mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA), including ground glass density, reticular changes, and honeycombing by quantitative imaging software.
2. **Safety**: Tolerability/safety will be assessed over the 28-week study period by the following parameters:
    - Incidence of AEs.
    - Incidence of serious adverse events (SAEs).
    - Incidence of respiratory AEs and SAEs.
    - Proportion of subjects discontinuing study drug due to AEs.
    - Change from Baseline in hematology and serum chemistries.
    - All-cause mortality.
    - Mortality due to respiratory deterioration.
3. **Disease related events associated with mortality**: The number of "respiratory decline" events over the 28-week study period as defined below:
    - Unscheduled visits to a healthcare professional for respiratory status deterioration.
    - Urgent care visits for respiratory status deterioration.
    - Hospitalization due to a worsening or exacerbation of respiratory symptoms.

    All "respiratory decline" events will be further characterized according to the definitions of IPF-related acute exacerbation, as proposed by an expert committee sponsored by the IPF Clinical Research Network and the National Heart Lung and

Blood Institute (NHLBI) (Collard, Moore et al. 2007) and applied by (Collard, Yow et al. 2013)

- Acute onset of symptoms (< 30 days in duration)
- New radiographic abnormalities (bilateral ground glass or consolidation on HRCT with no pneumothorax or pleural effusion)
- The absence of an identified infectious etiology by routine clinical practice
- Exclusion of alternative causes by routine clinical practice, including:
  a. Left heart failure
  b. Pulmonary embolism
  c. Identifiable cause of acute lung injury

4. **Pulmonary Function Tests**
   - Proportion (%) of subjects with a decline in FVC% predicted of ≥ 5% and ≥ 10% from Baseline to Week 28.
   - Proportion (%) of subjects with a decline in FVC in ml of ≥ 100ml and ≥ 200ml from Baseline to Week 28.
   - Proportion of subjects with an increase in FVC % predicted of ≥ 5% and ≥10% from Baseline to Week 28.
   - Proportion of subjects with an increase in FVC in ml of ≥ 100 ml and ≥ 200 ml from Baseline to Week 28.
   - Proportion of subjects with stable disease by FVC %, defined as a change in FVC % predicted of < 5% from Baseline to Week 28.
   - Proportion of subjects with stable disease by FVC in ml, defined as a change in FVC of < 100ml from Baseline to Week 28.
   - Mean change from Baseline to Week 28 in % predicted Hb-corrected diffusion capacity of carbon monoxide (DLCO).
   - Change in 6-minute walk distance, in meters, from Baseline to Week 28.

3.3. Exploratory Endpoints

The exploratory endpoints for the study include:

1. **Other Weeks**
   - Examine the change from Baseline at Weeks 4, 8, 12, 16, 20, 24 and 28for the FVC % predicted, FVC in ml, and 6MWT distance.
2. **Structural Imaging**
   - Transitions from Baseline to Week 28 between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and mild, moderate, and severe low attenuation areas) by quantitative imaging software.
   - Correlation of transitions between categories of lung features by quantitative imaging and changes in FVC% predicted.
   - Correlation of transitions between categories of lung features by quantitative imaging and changes in Hb-corrected DLCO.
   - Impact of inspiratory effort on results of HRCT quantitative imaging.

3. **Patient Reported Outcomes**
    - Change in Patient Reported Outcomes as measured by King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and Leicester Cough Questionnaire (LCQ) from Baseline to Week 28.
4. **Biomarkers**
    - Changes in serum and cellular biomarkers and response according to baseline genetic characteristics: including but not limited to TLR3, L412F polymorphism, and MUC5B promoter polymorphism.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

The current study is a Phase 2, randomized, double-blind, placebo-controlled, pilot study designed to evaluate the efficacy and safety of PRM-151 administered through Week 24 to subjects with IPF. Subjects meeting the eligibility criteria for the study will be randomized to PRM-151 10 mg/kg every 4 weeks or placebo. Efficacy will be evaluated through pulmonary function tests (PFTs), high resolution CT (HRCT), 6-minute walk test (6MWT), and Patient Reported Outcomes (PROs).

Subjects will be evaluated for study eligibility during Screening within 4 weeks before enrollment and Baseline assessments. Subjects who are determined to be eligible, based on Screening assessments, will be enrolled in the study and randomly allocated to treatment with PRM-151 or placebo. Subjects will receive study drug treatment for 24 weeks.
Approximately 117 subjects will be randomly assigned on a 2:1 basis to treatment with PRM-151 or placebo, as follows:

- PRM-151 10 mg/kg IV infusion over 60 minutes on days 1, 3, and 5, then one infusion every 4 weeks
- Placebo IV infusion over 60 minutes on Week days 1, 3, and 5, then one infusion every 4 weeks

The randomization will use a 2:1 ratio (PRM-151: placebo). The randomization will also be stratified according to other treatments for IPF (subjects receiving pirfenidone or nintedanib and subjects with no other treatment for IPF).
After completion of study treatment through Week 24, all subjects may receive PRM-151 10 mg/kg IV infusion over 60 minutes Days 1, 3, and 5, then once every 4 weeks for an indefinite period of time in an open label study extension. Dosing will be administered on Days 1, 3, and 5 will be repeated once every 28weeks during the extension.

4.1.1. Treatment Period: Efficacy-related Assessments

Subjects undergo testing on an every 4-week basis after randomization (occurring at Weeks 4, 8, 12, 16, 20, 24 and 28) for efficacy and safety.

During treatment, PFTs, 6MWT, and PROs will be performed on an every 4-week basis. HRCT will be performed on Day 1 as the Baseline assessment and again at Week 28. HRCT and PFTs must be done on the same day. PFTs will be reviewed centrally by reviewers blinded to treatment group and time point.

4.1.2. Treatment Period: Tolerability/Safety-Related Assessments

Adverse events (AEs) and concomitant medications will be assessed at all study visits. In addition, information regarding hospitalizations, emergency department visits, and unscheduled or urgent care visits to a health care provider due to a deterioration in respiratory status or symptoms will be collected at all study visits.

4.1.3. **Open Label Post-Study Treatment Extension**

4.1.4. **After completing 24 weeks of treatment, all subjects will be offered the option to receive PRM-151 in an open-label PRM-151 treatment extension period for an indefinite period of time.. All subjects will receive PRM-151 10 mg/kg IV Days 1, 3, 5 then every 4 weeks in the extension. Dosing on days 1, 3 and 5 will be repeated every 28 weeks during the extension. PROs, PFTs, spirometry and 6MWT will be done every 4 weeks for the first 24 weeks and then every 12 weeks. DLco, FRC &TLC by nitrogen washout method will be done every 12 weeks. HRCT will be done at 1.5 years (Week 76) and 2.5 years (Week 128) on the same day as DLco and FRC & TLC by nitrogen washout. Subjects are allowed to begin treatment with, restart treatment with or increase the dose of pirfenidone or nintedanib after the week 28 visit have been performed**

4.1.5.

4.1.6. **Study Duration**

Subjects will receive study drug for a minimum of 24 weeks. Subjects will participate in the study for up to 128 weeks, including a 4-week screening period, 24 week treatment period, an open-label treatment extension period for an indefinite period of time, and a 4 week follow up period.

5. SELECTION OF STUDY POPULATION

5.1. Study Population

5.1.1. Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

1. Subject must be 40-80 years of age at the time of signing the Informed Consent Form (ICF);
2. Subject has well documented IPF satisfying the ATS/ERS/JRS/ALAT diagnostic criteria (Raghu, Collard et al. 2011). In the absence of a surgical lung biopsy, HRCT must be "consistent with UIP" defined as meeting either criteria A, B, and C, or criteria A and C, or criteria B and C below:
    A. Definite honeycomb lung destruction with basal and peripheral predominance.
    B. Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance.
    C. Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern.
3. If on pirfenidone or nintedanib, subject must have been on a stable dose of pirfenidone or nintedanib for at least 3 months prior to screening without increase in FVC% predicted on two consecutive PFTs, including screening PFTs. Subjects may not be on both pirfenidone and nintedanib.
4. If not currently receiving pirfenidone or nintedanib, subject must have been off pirfenidone or nintedanib for ≥4 weeks prior to screening
5. Subject has a FVC ≥ 50% and ≤ 90% of predicted.
6. Subject has an Hb corrected and/or Hb uncorrected DLCO ≥ 25% and ≤ 90% of predicted.
7. Minimum distance on 6MWT of 150 meters.
8. Subject has a forced expiratory volume in 1 second (FEV_1)/FVC ratio > 0.70.
9. Women of child bearing potential (WCBP), defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if ≤55 years or 12 months if >55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use highly effective methods of birth control throughout the study and up to 30 days after the study for WOCBP and up to 90 days for partners of child bearing potential of male participants. Highly effective methods of contraception include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation by oral, intravaginal, or transdermal administration; progestogen-only hormonal contraception associated with inhibition of ovulation by oral, injectable, or implantable administration; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; partner vasectomy, and total abstinence (only if total abstinence is the preferred method and usual lifestyle of the subject). Adequate contraceptive use should be continued until 28 days after the final dose of the study drug.

10. Subject has a life expectancy of at least 9 months
11. Subject, according to the investigator's best judgment, can comply with the requirements of the protocol.
12. Subject and the treating physician considered all medicinal treatment options and / or possibly a lung transplantation prior to considering participation in the study
13. If the subject is on a lung transplant list, the Investigator anticipates the subject will complete the study prior to transplant.
14. Subject has provided written informed consent to participate in the study.

5.1.2. **Exclusion Criteria**

Subjects meeting any of the following exclusion criteria are not to be rolled in the study:

1. Subject has emphysema ≥ 50% on HRCT or the extent of emphysema is greater than the extent of fibrosis according to the reported results of the most recent HRCT.
2. Subject has a history of cigarette smoking within the previous 3 months.
3. Subject has received investigational therapy for IPF within 4 weeks before baseline.
4. Subject is receiving systemic corticosteroids equivalent to prednisone > 10 mg/day or equivalent within 2 weeks of baseline.
5. Subject received Immuno-suppressants (e.g. azathioprine, cyclophosphamide, or cyclosporine or other immunosuppressants including those used after organ transplant) within 4 weeks of baseline. Subject has a history of a malignancy within the previous 5 years, with the exception of basal cell skin neoplasms. In addition, a malignant diagnosis or condition first occurring prior to 5 years must be considered cured, inactive, and not under current treatment.
6. Subject has any concurrent condition other than IPF that, in the Investigator's opinion, is unstable and/or would impact the likelihood of survival for the study duration or the subject's ability to complete the study as designed, or may influence any of the safety or efficacy assessments included in the study.
7. Subject has baseline resting oxygen saturation of < 89% on room air or with supplemental oxygen.
8. Subjects that are unable to refrain from use of the following:
    a. Short acting bronchodilators on the day of and within 12 hours of pulmonary function, DLco, and 6-minute walk assessments.
    b. Long acting bronchodilators on the day of and within 24 hours of these assessments.
9. Subject has a **known** post-bronchodilator (short-acting beta agonist [SABA] – albuterol or salbutamol) increase in FEV_1 of >10% and in FVC of >7.5%.
10. Female pregnant and/or lactating subject.

5.2. Withdrawal and Replacement of Subjects

The Investigator may withdraw a subject from the study for any of the following reasons:

- Subject, Investigator, or Sponsor request.
- Protocol violation.
- AE.
- Pregnancy (mandatory).
- Progression of disease that, in the opinion of the Investigator, precludes further study drug treatment.
- Subject decision. A subject may withdraw consent to participate in the study at any time.

The reason for study withdrawal is to be documented in the subject's source documents and electronic case report form (eCRF).

5.3. Study Termination

If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- Site-specific inability of an Investigator to enter subjects at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.
- A decision on the part of the Sponsor to suspend or discontinue the study for administrative reasons.

5.4. Subject Management

This study will be conducted on an out-patient basis.

Subjects will be evaluated for study eligibility during the Screening period within 4 weeks before the first study drug dose. All subjects must provide written informed consent before any study specific samples are collected or evaluations performed in this study.

Subjects who are determined to be eligible for the study will be enrolled and randomly assigned to treatment at Baseline (Week 0). For the purposes of this study, enrollment is defined as randomization.

Subjects are allowed to begin treatment on pirfenidone or nintedanib after week 28 visit is performed. .

During the 24-week treatment period, subjects are to attend study center visits on Days 1, 3 and 5 then an every 4-week basis at Weeks 4, 8, 12, 16, 20, and 24 (±3 days) for study-related efficacy assessments and dosing.

After completing treatment through week 24, subjects will be offered the option to continue PRM-151 in an open-labeled treatment extension for an indefinite period of time.

An End of Study visit is to be conducted 4 weeks (±3 days) after the last dose of study drug (Week 28 for the main study and upon completion for the open label extension).

5.5. Investigator Compliance

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol.

5.6. Subject Adherence

All subjects are required to adhere to the protocol-specified visit schedule. If a subject misses a scheduled visit, attempts should be made to reschedule the visit within the visit windows described above. Failure to attend scheduled study visits may result in discontinuation from the study.

5.7. Data Monitoring Committee

A blinded DMC will be established to review safety data from this study, thereby better ensuring the safety of study participants. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will be constituted of independent clinicians' expert in the field of IPF and clinical research. A formal charter will be established for the conduct of the DMC.

The committee is planned to review the safety data in a blinded manner, but a procedure will be in place to allow the committee an immediate unblinding of either specific cases or of the whole study in case of detection of a potential safety signal necessitating an unblinded review of some (or all) subjects.

6. STUDY TREATMENT(S)

6.1. Investigational Product

All study drugs are for investigational use only and are to be used only within the context of this study. All study drugs will be supplied by Promedior.

6.2. Treatment(s) Administered

Subjects will be randomized to receive the study drug PRM-151 or placebo. Subjects randomized to placebo will receive intravenous (IV) infusions of sterile saline solution over 60 minutes. Please refer to the Pharmacy Manual for more detail.

Subjects randomized to study drug will receive intravenous (IV) infusions of 10 mg/kg PRM-151 over 60 minutes, with dose based on the subject's baseline weight. Refer to the Pharmacy Manual and the Investigator's Brochure for detailed instructions on special precautions and handling and requirements for weight based dose recalculations.

On all dosing days, dosing will occur ***after*** all safety and efficacy assessments scheduled for that visit are completed

Medical personnel authorized by the Investigator will be responsible for the administration of study drug and for observation of each subject throughout the study. Subjects should be observed for one-hour post infusion to monitor for infusion related reactions.

In the case of occurrence of signs and symptoms consistent with infusion related reaction, follow institutional protocol and reduce the rate of infusion of PRM-151 to half the initial rate; consider discontinuing infusion of PRM-151 if symptoms do not respond immediately to medical intervention. If signs and symptoms do not resolve immediately by slowing the infusion, discontinue infusion of PRM-151. If signs and symptoms resolve with intervention including discontinuation of PRM-151, PRM-151 infusion may be restarted at half the initial rate.

In the event of an infusion related reaction (IRR) beginning after treatment on Baseline, an ECG is performed and a blood sample for cytokines is collected as soon as possible after stabilization of the subject.

If PRM-151 resulted in an infusion related reaction, during a prior administration, use the following premedication for all subsequent PRM-151 administration:

- 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 long-acting corticosteroid

No other dose modifications are required per protocol. The investigator should use his/her medical judgment in the case of adverse events that may require a dose interruption. If the subject is not able to adhere to the original dosing schedule, the subject should be dosed as soon as possible within 2 weeks of the scheduled visit. If the subject dosing is >2 weeks sponsor should be consulted.

6.3. Method of Assigning Subjects to Treatment Groups

Subjects who are candidates for screening into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria initially have been satisfied. The Unblinded Pharmacist will register the subject in the IVRS system, and the IVRS system will assign a sequential and unique subject number. Once a subject number has been assigned, it cannot be reused.

Prior to randomization, the Investigator will ensure that the subject continues to meet the inclusion and exclusion criteria and is eligible for study participation.

Once a subject is deemed by the Investigator to be eligible, the unblinded pharmacist will access the IVRS system for randomization and study drug assignment.

6.4. Blinding

All study personnel, with the exception of the unblinded site pharmacist, will be blinded to the treatment allocation a subject is randomized to. It is imperative that this blinding be maintained during the dispensing of investigational product.

6.4.1. Procedures for Breaking the Blind

The treatment assignment must not be broken during the study except in emergency situations where the identification of study drug is required for further treatment of the subject. Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, the Investigator should use his/her best judgment as to whether to unblind without first attempting to contact the Medical Monitor to discuss and agree to the need for unblinding. If the Investigator determines that it is not necessary to unblind immediately, he/she will first attempt to contact the Medical Monitor to discuss and agree to the need for unblinding. If the Investigator has tried but is unable to reach the Medical Monitor, he/she should use his/her best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the Medical Monitor.

6.5. Study Drug Supply

PRM-151 Solution for Injection is a 20 mg/mL solution of PRM-151 in 10 mM sodium phosphate, 5% (w/v) sorbitol, and 0.01% (w/v) polysorbate 20 with a pH of 7.5. Each vial of PRM-151 Solution for Injection contains 160 mg of PRM-151 in 8.0 mL of solution.

Placebo consists of an infusion of sterile physiologic saline, matched to PRM-151 in total volume.

6.6. Packaging and Labeling

PRM-151 is supplied in 10 ml single use vials as a clear to opalescent, sterile 20.0 mg/mL solution 10 mM sodium phosphate, 5% (w/v) sorbitol, and 0.01% (w/v) polysorbate 20 with a pH of 7.5. Each vial contains 8 ml PRM-151 (160 mg of PRM-151).

Study drug will be labeled investigational. Study drug labels will not bear any statement that is false or misleading in any manner or represents that the study drug is safe or effective for the purposes for which it is being investigated.

6.7. Storage and Accountability

PRM-151 will be provided to the clinical site in a temperature controlled, monitored container. Investigational product should be stored under refrigerated conditions (2°C-8°C [35.6°F-46.4°F]) and protected from light. Vigorous mixing or vortexing should be avoided.

Investigational product will be dispensed at the study site and stored in a locked storage area. The disposition of all investigational product delivered to a Principal Investigator must be recorded on a subject-by-subject basis by completing the Clinical Trial Material Accountability Log. The date and time of administration of the investigational product must be documented on the appropriate eCRF.

The unblinded pharmacist must ensure that all documentation regarding investigational product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

All packing slips and other shipment documentation must be retained as well as any investigational product return forms. See the Pharmacy Manual for additional details.

6.8. Rationale for the Dose(s) Selected

In a multiple ascending dose study (PRM151F-12GL), PRM-151 administered IV on Days 1, 3, 5, 8, and 15 to subjects with IPF was well tolerated at doses up to 10 mg/kg. Plasma levels of PRM-151 (C_{max} and AUC) were dose proportional across the range of doses from 1 to 10 mg/kg. PRM-151 had a half-life of 21 to 44 hours. The study did not demonstrate a dose response, but was not intended to do so. Based on these findings, a PRM-151 dose of 10 mg/kg was selected for investigation in the current study. Preclinical dose ranging studies and in vitro potency assays indicate that the effective dose range in humans may be .2-10 mg/kg. Ten mg/kg was selected for this study because it was safe and resulted in a reduction in bone marrow fibrosis in 11 out of 24 subjects with myelofibrosis treated with PRM-151 10 mg/kg either weekly or every 4 weeks.

7. STUDY PROCEDURES

Detailed descriptions of subject evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study as described in Section 7 and in the Schedule of Events (Appendix A).

All data collected are to be recorded on source documents and entered into the appropriate eCRF page.

The Investigator at the clinical trial site is responsible for maintaining a record of all subjects pre-screened, screened, and enrolled into the study.

All subjects must provide written informed consent before the performance of any study procedures.

7.1. Informed Consent

Prior to conducting any study-related procedures, written informed consent must be obtained from the subject or the subject's legally authorized representative.

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject by the Investigator or designee in accordance with the guidelines described in Section 9.1. Documentation and filing of informed consent documents should be completed according to Section 10.5.

7.2. Study Entrance Criteria

At Screening, each subject assessed for eligibility against the study entrance criteria. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented.

7.3. Demographics

Subject demographic information including gender, age, date of birth, race, ethnicity and number of years since diagnosis of IPF will be collected prior to the subject receiving the first dose of PRM-151.

7.4. Past Medical History

Medical history will be recorded in the eCRF. Any relevant and/or significant previous or existing medical condition(s) that occurred within 5 years prior to time of informed consent) should be reported as medical history. Prior and current therapies for IPF will be recorded in the eCRF.

7.5. Height and Weight

Height will be recorded at Screening for all subjects. Weight will be recorded at all dosing visits for all subjects.

7.6. Laboratory Variables

Clinical laboratory tests will be performed by the local clinical laboratory facility.

7.6.1. Hematology and Clinical Chemistries

Blood samples for hematology, clinical chemistries and coagulation are to be collected as per the schedule of events (Appendix A).
The following laboratory variables are to be measured:

Hematology; Hematocrit, Platelet count, White blood cell (WBC) count, Red blood cell (RBC) count, Hemoglobin, Lymphocytes, Eosinophils, Neutrophils, Monocytes, Basophils.

Serum Chemistries and Liver Function Tests; Chloride, Potassium, Blood urea nitrogen (BUN), Creatinine, Albumin, Aspartate aminotransferase (AST), Total bilirubin, Sodium, Bicarbonate (CO_2), Calcium, Glucose, Alkaline phosphatase (ALK), Alanine aminotransferase (ALT), Total protein.

Coagulation Tests: Prothrombin time (PT), Partial Thromboplastin time (PTT), International Normalized Ratio (INR)

7.6.2. ECG and Cytokines

ECG and cytokines will be collected at baseline prior to PRM-151 dosing. Following the baseline assessment, ECG and cytokines will only be collected in the event of an infusion related reaction (IRR) as soon as possible after stabilization of the subject.

7.6.3. Pregnancy Testing

Serum pregnancy testing is required for female subjects of child-bearing potential. A female of childbearing potential is a sexually mature woman who has not undergone a hysterectomy, bilateral oophorectomy, or tubal ligation or is not naturally postmenopausal (i.e., has had menses at any time within the previous 24 months).

Pregnancy testing is to be performed during Screening. Pregnancy testing should be repeated during treatment any time pregnancy is suspected.

During Screening, results must be reviewed and confirmed to be negative for the subject to be eligible for enrollment in the study. If positive pregnancy test results are obtained after the start of study drug treatment, study drug is to be unblinded and discontinued. Pregnancies are to be reported and followed as described above.

7.7. Physical Examination

A complete physical examination is to be performed during Screening and an abbreviated physical exam thereafter. The complete physical examination is to include measurement

of height during Screening. Weight is to be measured throughout the study for use in weight based dose calculations.

Complete physical examinations also will include a review of the following body systems:

- General appearance.
- Head, eyes, ears, nose, and throat.
- Respiratory.
- Cardiovascular.
- Abdomen.
- Neurologic.
- Extremities.
- Dermatologic.

Full physical examinations are to be performed at screening; Abbreviated physical exams are to be performed thereafter.

The findings of each examination are to be documented in the eCRF.

If an abnormality noted on physical examination is considered by the Investigator to be clinically significant, then the abnormality is to be recorded as part of the subject's medical history if occurring prior to start of dosing and as an AE occurring if after the start of study drug administration at Week 0, where the finding represents a change from Baseline. Any worsening of a baseline medical condition during the study should be recorded as an adverse event.

7.8. Vital Signs

Vital signs, including measurement of systolic and diastolic blood pressure, pulse, heart rate, and O_2 saturation, are to be measured in the sitting position as per the schedule of events (Appendix A). At dosing visits, vital signs will be measured pre-dose as well as 1 hour post-dose and entered into the eCRF. Vitals signs should be monitored every 15 minutes during the infusion and captured on the source document.

If a vital sign abnormality is considered by the Investigator to be clinically significant, then the abnormality is to be recorded as part of the subject's medical history if occurring prior to start of dosing and as an AE occurring if after the start of study drug administration at Week 0, where the finding represents a change from Baseline.

7.9. Concurrent Medications

All prescription and non-prescription medications including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 4 weeks prior to the first dose of PRM-151 through the last study visit must be recorded in the eCRF.

If on pirfenidone or nintedanib, subject must have been on a stable dose of pirfenidone or nintedanib for at least 3 months prior to screening without increase in FVC% predicted on two consecutive PFTs, including screening PFTs. If subjects are currently on a stable dose of pirfenidone they are allowed to stop taking pirfenidone while remaining in the study but are not allowed to start dosing with nintedanib. If subjects are currently on a stable dose of nintedanib they are allowed to stop taking nintedanib while remaining in the study but are not allowed to start dosing with pirfenidone.

7.9.1. Prohibited Concurrent Medications

The following medications are prohibited during the study:

- All investigational therapies other than PRM-151for any indication, including therapies that are approved in other indications that are being investigated in IPF, are prohibited within 4 weeks before Screening and during study participation.
- Inhaled or systemic corticosteroids. (Low dose [≤10 mg daily] corticosteroids are permissible, provided the dose has been stable for 30 days prior to Baseline.)
- Bronchodilators:
- Short-acting bronchodilator use within 12 hours of pulmonary function, DLco, and 6MWT assessments.
- Long acting bronchodilators are disallowed the day of and within 24 hours of pulmonary function testing, DLco, and 6MWT assessments.
- The use of inhaled bronchodilator agents at times outside these windows is permissible.
- Immuno-suppressants (e.g. methotrexate, azathioprine, cyclophosphamide, cyclosporine, everolimus or other immunosuppressants including those used after organ transplant) are prohibited within 4 weeks of baseline and during the study.

7.10. Efficacy Measurements

On all dosing days, dosing will occur after all safety and efficacy assessments scheduled for that visit are complete.

7.10.1. Pulmonary Function Tests

Spirometry will be measured according to ATS guidelines (Miller, Crapo et al. 2005a), as per the schedule of events (Appendix A).

DL_{CO} is to be measured using the single-breath technique according to ATS/ERS guidelines (MacIntyre, Crapo et al. 2005) at Screening, Baseline and at Week 28, and weeks 76 and 128 visits for subjects continuing treatment in the extension. Diffusion capacity should be done on the same day as HRCT.

Lung volumes (TLC and FRC) using Nitrogen washout method (Wanger, Clausen et al. 2005) will be performed at Screening, Baseline and Week 28, and weeks 76 and 128 visits for subjects continuing treatment in the extension.

PFTs will be reviewed centrally by reviewers blinded to treatment group and time point.

7.10.2. Six-minute Walk Test

Exercise tolerance will be evaluate during the 6MWT according to ATS guidelines (ATS 2002) (Appendix B) as per the schedule of events (Appendix A). If possible, 6MWT

should be the last efficacy assessment completed, by the subject. If it is not possible to complete the 6MWT last, then allow a 30-minute recovery time before continuing with the next efficacy assessment. During the open-labeled extension, subjects will have 6MWT measured every twelve weeks.

7.10.3. High-resolution Computed Tomography

High-resolution Computed Tomography (HRCT) will be performed at the Baseline and Weeks 28, and weeks 76 and 128 visits for subjects continuing treatment in the extension.

Spirometry will be performed at selected sites to ensure that full inspiration HRCT is at Total Lung Capacity (TLC).

HRCT is to be performed with the subject in the supine position and at full inspiration. Contiguous CT volumetric acquisition will be obtained according to a specified protocol. HRCT scans will be compared using a standardized reading protocol and software to assess treatment-related changes in lung fibrosis.

7.10.4. Patient Reported Outcomes

Kings Brief Interstitial Lung Disease questionnaire (K-BILD) (Patel, Siegert et al.)(Appendix D) is a disease specific questionnaire validated to look at the health status of subjects with a variety of forms of interstitial lung disease (ILD). It consists of 15 items. The K-BILD questionnaire will be performed as per the schedule of events (Appendix A). If possible, the questionnaire should be the first assessment completed by the subjects.

Leicester Cough Questionnaire (Birring, Prudon et al. 2003) (Appendix E) a self-completed health related quality of life measure of chronic cough. The LCQ total score ranges from 3 to 21 and from 1 to 7 for physical, psychological and social domains; a higher score indicates a better health-related quality of life. The LCQ questionnaire will be performed as per the schedule of events (Appendix A). If possible, the questionnaire should be the first assessment completed by the subjects.

7.10.5. Pentraxin-2 Levels

Blood samples for determination of pentraxin-2 levels are to be collected pre-dose as per the schedule of events (Appendix A).

7.10.6. Anti-Pentraxin 2 antibodies / Anti-Drug Antibodies (ADA)

Blood samples for determination of ADA levels are to be collected pre-dose as per the schedule of events (Appendix A).

7.11. Biomarker Assessments

7.11.1. Baseline Genetic Status

The subject's baseline genetic status for TLR3, L412F polymorphism, and MUC5B promoter polymorphism will be collected at Baseline, if available. If the subject has not previously been tested for these genetic characteristics, a blood sample for this analysis should be drawn at baseline.

7.11.2. Blood Sample Collection for Biomarker Assessment

Blood samples to study exploratory serum and cellular biomarkers are to be collected pre-dose at Baseline, Week 28 and at Week 128 of the open label extension.

7.12. Safety Measurements

7.12.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to study drug.

All AEs from signing of informed consent until last study visit will be entered in the database. For those subjects prematurely withdrawn, TEAEs will be monitored until, at least, 4 weeks from last study treatment dose or resolution of AE, whichever is earlier

7.12.1.1. Respiratory Decline Events

For the purposes of this study, such "respiratory decline" events are defined as follows:

- Unscheduled visits to a healthcare professional for respiratory status deterioration.
- Urgent care visits for respiratory status deterioration.
- Hospitalization due to a worsening or exacerbation of respiratory symptoms.

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

- Acute onset of symptoms (< 30 days in duration)
- New radiographic abnormalities (bilateral ground glass or consolidation on HRCT with no pneumothorax or pleural effusion)
- The absence of an identified infectious etiology by routine clinical practice
- Exclusion of alternative causes by routine clinical practice including:
  a. Left heart failure
  b. Pulmonary embolism
  c. Identifiable cause of acute lung injury

7.12.1.2. Infusion related reactions

In the event of acute hypersensitivity or other infusion reaction, institutional protocol should be initiated, ECG should be performed, and a blood sample drawn for cytokines. Signs and symptoms of an infusion reaction may include the following: headache, fever, facial flushing, pruritis, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, hypotension, lightheadedness, palpitations, urticaria and somnolence. Although unlikely, serious allergic reactions (e.g., anaphylaxis) may occur at any time during the infusion.

In the case of Grade 2 occurrence of signs and symptoms consistent with infusion related reaction, follow institutional protocol and reduce the rate of infusion of PRM-151 to half the initial rate; consider discontinue infusion of PRM-151 if symptoms do not respond to medical intervention. If signs and symptoms resolve with intervention including discontinuation of PRM-151, PRM-151 infusion may be restarted at half the initial rate.

In the case of Grade 3 or greater occurrence of signs and symptoms consistent with infusion related reaction, discontinue infusion of PRM-151.

In the event of an infusion related reactions, an ECG should be performed and a blood sample for cytokines should be collected as soon as possible after stabilization of the subject.

If PRM-151 resulted in signs and symptoms consistent with Grade 2 or 3 Infusion related reaction, infuse PRM-151 over 120 minutes and use the following premedication for all subsequent PRM-151 administration:

- 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)

Infusion related reactions must be reported to Promedior as described in section 7.12.4.1, Reporting of Adverse Events of Special Interest.

7.12.1.3. Adverse Drug Reaction

A suspected adverse drug reaction (ADR) is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Health Authority safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

7.12.1.4. Unexpected Adverse Event

An unexpected AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.12.1.5. Serious Adverse Event

An AE or suspected ADR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction

which hypothetically might have caused death had it occurred in a more severe form.
- In-subject hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned).
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in -subject hospitalization, or the development of drug dependency or drug abuse.

7.12.2. Adverse Event Assessment

All AEs from signing of informed consent until last study visit will be entered in the database, but only AEs occurred from the time of first study treatment dose administered to the subject (TEAEs) until last study visit will be analysed (see 7.12.1). This includes AEs the subject reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during scheduled study center visits.

Each AE is to be assessed by the Investigator with regard to the following categories.

Serious/Non-Serious

Adverse events that meet the criteria specified above are to be considered serious.

Relationship to Study Drug

Relationship of an AE or SAE to investigational product is to be determined by the Investigator based on the definitions in Table 7-1.

Table 7-1: Adverse Event Relatedness

Relationship to Study Drug	Definition
Not Related	Unrelated to investigational product
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.

Intensity

The Investigator is to determine the intensity of the AE according to the criteria in Table 7-2.

Table 7-2: Adverse Event Grading

Severity	Definition
Grade 1 (Mild):	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate):	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3 (Severe):	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 (Life-threatening):	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Death):	Death related to AE.

7.12.3. Recording Adverse Events

Only TEAEs will be recorded (see 7.12.1). All AEs, regardless of relationship to study drug, are to be recorded in the Adverse Events eCRF. All AE reports are to contain the

following details regarding the AE: a brief description, onset date, duration, intensity, treatment required, relationship to study drug, study drug action taken, outcome, and whether the event is classified as serious.

7.12.4. Reporting Serious Adverse Events

Only serious TEAEs will be recorded (see 7.12.1). The Investigator must report all SAEs to the Safety Unit [redacted] within 24 hours of discovery either by e-mail or fax to:

- [redacted]
- [redacted]
- [redacted]

A completed SAE report is to be sent to [redacted] Safety Unit within 24 hours of discovering the event. The initial report should include at least the following information:

- Subject's study number;
- Description and date of the event;
- Criterion for serious; and
- Preliminary assignment of causality to study drug.

The Safety unit will contact the Investigator either by email or telephone for follow-up information regarding the SAE, as appropriate.

7.12.4.1. Reporting Adverse Events of Special Interest

The Investigator must report suspected Infusion Related Reaction, regardless of severity, on an Adverse Event of Special Interest (AESI) form. This form must be completed and submitted, either by e-mail or fax to [redacted] Drug Safety Unit, immediately but no later than 24 hours of the Investigator's learning of the event to [redacted] Safety Unit:

- [redacted]
- [redacted]
- [redacted]

7.12.4.2. Follow-Up of Adverse Events

The Investigator must continue to follow all SAEs and non-serious AEs considered to be reasonably or possibly related to study drug either until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

7.12.4.3. Reporting Safety Information

The Investigator must promptly report to his or her IRB/EC all unanticipated problems involving risks to subjects. This includes death from any cause and all SAEs reasonably or possibly associated with the use of study drug according to the IRB/EC's procedures.

7.12.4.4. Protocol Deviations Due to an Emergency or Adverse Event

In the event of an emergency, the investigator or other physician should use their medical judgment and do what is best for the subject, 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 subject should continue to participate in the study. All protocol deviations and reasons for such deviations must be documented.

7.12.5. Reporting Pregnancies

Pregnancy itself is not considered an AE. If a subject becomes pregnant or the partner of a subject participating in the study becomes pregnant during the study or within 28 days of discontinuing any study drug, The Investigator should report the pregnancy on a separate pregnancy report form provided to the sites. Only pregnancies occurring from the time of first study treatment dose administered to the subject will be reported and documented. The study treatment will be immediately discontinued for any female subject who becomes pregnant during study participation, if study treatment is ongoing at that time.

The subject/partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy.

This pregnancy report form must be completed and submitted, either by e-mail or fax, immediately but no later than 24 hours of the Investigator's learning of the event to [redacted]Safety Unit:

- [redacted]
- [redacted]
- [redacted]

However, any pregnancy complication, spontaneous or elective abortion, still birth, neonatal death, or congenital anomaly will be recorded as an AE or SAE, and reported, as applicable.

8. STATISTICAL ANALYSES

8.1. Statistical Basis for Sample Size

The primary objective is not to formally demonstrate the superiority of PRM-151 over placebo, but to provide a reliable estimate of the size of the effect of PRM-151 on absolute change from baseline to 28 weeks in mean FVC% predicted, hereafter referred to as the primary endpoint. Nevertheless, the sample-size has been calculated to ensure a sufficient power to demonstrate the efficacy of PRM-151 over placebo on the primary endpoint under a set of hypotheses on effect sizes in the two groups and on the variability of the primary endpoint.

The primary endpoint will be tested in a model with two types of subjects: subjects on a stable dose of pirfenidone or nintedanib, and subjects not on other treatment for IPF.
The sample size calculation is based on the following assumptions:

- Primary endpoint is normally distributed
- Homogeneity of variance, i.e. the standard deviation is the same in both arms, and for both types of subjects.
- Randomization ratio PRM-151: placebo equals 2:1.
- Expected value of the primary endpoint for subjects on pirfenidone or nintedanib will be -1.5.
- Expected value of the primary endpoint for subjects on no other treatment will be -3.
- Expected value of the primary endpoint for subjects on PRM-151 will be $\geq$ 0.75.
- Standard deviation of the primary endpoint is 5
- 75% of subjects will be on a stable dose of pirfenidone or nintedanib
- 25% of subjects will not be on other treatment for IPF
- Significance level (α)=0.10 two-sided.
- Desired power to demonstrate superiority is 80%

A sample size of one hundred and two (102) evaluable subjects in total (68 PRM-151 and 34 placebo) is enough to demonstrate superiority at $p<0.10$ with a power of 80% under the above assumptions. Assuming a non-evaluability rate of about 15%, 117 subjects in total (78 PRM-151 and 39 placebo) are to be enrolled. Stratified randomization will ensure a balance of PRM-151: placebo in subjects on pirfenidone or nintedanib and not on any other therapy, with at least 25% of subjects on no other therapy.

8.2. General considerations for statistical analysis

8.2.1. Statistical Analysis Plan

The statistical section of the protocol presents the main features of the planned statistical analysis. A detailed statistical analysis plan (SAP) will be prepared by the Venn Life Sciences statistician, validated by the sponsor and signed before the database lock prior to any unblinded statistical analysis.

Any change to the planned statistical methods will be documented in the clinical study report.

8.2.2. Descriptive statistics

Quantitative variables will be described by treatment group using the following statistics: number of available data, number of missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum values. When relevant, confidence intervals will also be computed.

Qualitative variables will be described by treatment group using number of available data, number of missing values, frequency counts for each category and corresponding percentage. Percentages will be calculated using the number of available data as the denominator (i.e. not including missing values). When relevant, confidence intervals will also be computed.

8.2.3. Inferential statistics

For the primary efficacy analysis, the overall type-one error rate will be set to 0.10 two-sided. There will be one single primary efficacy analysis, from which the conclusions on efficacy will be drawn. Consequently, there is no issue of multiplicity of primary analyses and no need to adjust the significance level.

Additional inferential tests will be computed for secondary efficacy analyses. No adjustment of the type-one error rate will be conducted. As a consequence, the results of these tests will have to be interpreted bearing in mind the issue of multiplicity and the increased risk of erroneously obtaining statistically significant results. Missing, Unused, and Spurious Data

Except for the use of LOCF for the analysis of the primary criterion as described below in Sections 8.5.1.1 and 8.5.1.2, all other analyses will be based on observed data only; no data will be imputed.

8.2.4. Interim Analyses

There is no interim analysis planned.

8.2.5. Software used for statistical analyses

The SAS software, version 9.2 or higher, will be used for the statistical analysis.

8.3. Protocol deviations

Major protocol deviations are defined as deviations liable to prevent or change the interpretation of the results of the primary efficacy analysis of the study. The following deviations will be considered as major (this list is not exhaustive and will be reviewed at the time of the blind review meeting):

- noncompliance with the inclusion or non-inclusion criteria
- noncompliance with study treatment
- no post-baseline data for the primary efficacy endpoint
- intake of forbidden medication

All other deviations will be considered as minor deviations. However, all deviations will be reviewed and adjudicated as either major or minor during the blind review meeting before database lock and code break.

8.4. Analysis datasets

The statistical analysis will be conducted on the following subject data sets:

The Full Analysis Set (FAS) will consist in all randomized subjects having received at least one administration of the study medication with at least one post-baseline assessment of FVC% predicted (primary efficacy criterion) available

The full analysis set will be the primary population for the efficacy analyses in this trial.

The Per Protocol (PP) set: a subset of the FAS composed of all subjects treated with the IMP, having received at least the planned IMP infusions on days 1, 3, 5, and weeks 4, 8 and 12 and who did not present any major protocol deviations.

The per-protocol set will be used for secondary analyses of the primary efficacy criterion and for the analysis of some selected secondary efficacy criteria.

The Safety (SAF) dataset: composed of all randomized subjects having received at least one dose of study drug. This data set will be used to perform the analysis of safety.

8.5. Planned Statistical analyses

8.5.1. Efficacy Analyses

8.5.1.1. Primary analysis of efficacy

The primary efficacy criterion is change from baseline to Week 28 in FVC% predicted

The comparison of PRM-151 with placebo will be carried out via a 2-sided statistical test with a type-one error rate of 0.10.

The two treatment arms will be compared using analysis of variance (ANOVA), with change from baseline to Week 28 in FVC% predicted as dependent variable (outcome), and treatment and stratum, as explanatory variables.

In case of missing measurement of FVC% predicted at week 28, the last available post baseline measurement will be carried forward.

The following statistical hypotheses will be tested:

•H0:Absence of difference between the treatment groups.

•H1:A difference exists between the treatment groups.

Least square means for changes from baseline to Week 28 in FVC% predicted, together with their 2-sided 95% confidence interval will be presented for both treatment groups. The mean difference between the two groups will also be presented with its 2-sided 90% confidence interval.

Due to the number of sites planned to recruit and randomize subjects in the study, it is expected that each site will include too few subjects to allow the inclusion of study site as a covariate in the stratification and the analysis,

8.5.1.2. Sensitivity analyses on the primary endpoint:

Sensitivity analyses on the FAS:

The mean changes from baseline to Week 28 in FVC% predicted will be compared between treatment groups on the FAS using an ANOVA model with treatment group and stratum as main effects and with a treatment by stratum interaction term as explanatory variables. This analysis will use the same method of data imputation for missing data (Last Observation Carried Forward, LOCF) as described in Section 8.5.1.1.

In case of a significant qualitative treatment by stratum interaction, the data will be carefully examined searching for a potential explanation and the conclusions of the primary efficacy analysis will have to be interpreted cautiously.

Potential differences in treatment effect according to study site will be addressed by tabulating the results on the primary criterion by treatment site, but it is expected that due to the small number of subjects within each site no precise estimates of within site treatment effect will be obtained for most of the sites.

Sensitivity analyses on the PP set:

The ANOVA model described above (see Section 8.5.1.1) for the primary efficacy analysis will be used for the analysis of the primary efficacy endpoint on the PP analysis set.

8.5.1.3. Secondary efficacy analyses:

8.5.1.3.1. Analyses of quantitative secondary and exploratory efficacy endpoints:

A similar analysis as described for the primary endpoint in Section 8.5.1.1 will be done for the secondary and exploratory efficacy variables, replacing FVC % predicted with the other variables as appropriate. These analyses will be conducted on the FAS and Per Protocol set.

FVC% predicted will also be analysed separately for each level of the stratum variable (in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF) using analysis of variance (ANOVA), with change from Baseline to week 28 in FVC% predicted as dependent variable (outcome), and treatment as the explanatory variable.

8.5.1.3.2. Analyses of quantitative primary, secondary and exploratory efficacy endpoints evolution over time:

The evolution of each efficacy variable with time will be compared between the two groups using a likelihood-based Mixed effects Model for Repeated Measures (MMRM) including treatment, stratum and time as fixed factors, the time by treatment interaction, the baseline (Day 1) measurement as covariate and the subject effect as a random effect to adjust for correlated errors over time. This analysis will be conducted on the FAS for all secondary and exploratory efficacy endpoints and on both the FAS and PP set for FVC % predicted.

8.5.1.3.3. Analyses of categorical secondary and exploratory efficacy endpoints:

Percentages of subjects in each category will be computed per treatment group.

The two treatment groups will be compared using a stratified statistical test (Cochran-Mantel-Haenszel general association test in SAS Freq procedure), adjusting for the Stratum effect. If the assumptions underlying the use of the asymptotic test are not met, the exact version of the test will be used.

8.5.2. Safety Analyses

AEs will be coded by using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number and percent of AEs reported, the number of subjects reporting each AE, and the number of subjects with any AE. A by-subject AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Safety data, including laboratory evaluations and vital signs assessments, will be summarized by time of collection and by treatment group. In addition, change from Baseline to any post-dose values will be summarized for vital signs and clinical laboratory results.

The frequency of subjects with abnormal safety laboratory results will be tabulated by treatment.

8.5.3. Other Analyses

8.5.3.1. Subject Disposition

A listing and table of proportions of subjects discontinuing the study for each reason will be provided by treatment / dose group. Details will be included in the Statistical Analysis Plan.

8.5.3.2. Demographic and Baseline Characteristics

Summary statistics will be provided for the demographic and baseline characteristics; details will be in the Statistical Analysis Plan.

8.5.3.3. Subject Adherence

Compliance with study drug will be computed for each subject as proportion of prescribed study drug actually taken. Details will be included in the Statistical Analysis Plan.

8.5.3.4. Concomitant Medications

A listing and table of proportions of subjects taking each concomitant medication will be provided. Details will be included in the Statistical Analysis Plan.

9. ETHICAL, LEGAL, AND ADMINISTRATIVE CONSIDERATIONS

9.1. Good Clinical Practice

This study will be conducted according to the protocol and in compliance with GCP, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

The Investigator confirms this by signing the protocol.

9.2. Informed Consent

Written informed consent in compliance with 21 Code of Federal Regulations (CFR) § 50 and/or ICH will be obtained from each subject prior to undergoing any protocol-specific tests or procedures that are not part of routine care.

Promedior will provide an informed consent form (ICF) template to the Investigator for use in developing a study center-specific ICF. Prior to submission of the study center-specific ICF to the IRB/EC, the study center-specific ICF must be reviewed and approved by Promedior. Any changes requested by the IRB/EC must also be approved by Promedior. The final IRB/EC-approved ICF must be provided to Promedior. Revisions to the ICF required during the study must be approved by Promedior, and a copy of the revised ICF provided to Promedior.

Before recruitment and enrollment, each prospective subject (or legal guardian) will be given a full explanation of the study and be allowed to read the ICF. After the Investigator or Sub-investigator is assured that the subject/legal guardian understands the commitments of participating in the study, the subject/legal guardian will be asked to sign and date the ICF.

A copy of the fully signed and dated ICF will be given to the subject. The original will be maintained in the subject's medical record at the study center. All active subjects will sign an updated ICF if revisions are made to the ICF during the course of the study.

9.3. Institutional Review Board/Ethics Committee

The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at study centers where IRB/EC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the Investigator.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB/EC as appropriate. The Investigator must submit written approval to Promedior or designee before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/EC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB / EC upon receipt of amendments and annually, as local regulations require.

The Investigator is also responsible for providing the IRB/EC with reports of any reportable serious ADRs from any other study conducted with the investigational product. Promedior will provide this information to the Investigator.

Progress reports and notifications of reportable serious ADRs will be provided to the IRB/EC according to local regulations and guidelines.

To ensure compliance with GCP and all applicable regulatory requirements, Promedior or designee may conduct a quality assurance audit.

9.4. Amending the Protocol

Any changes in this research activity, except those to remove an apparent immediate hazard to the subject, must be reviewed and approved by Promedior and the IRB/EC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB/EC for approval prior to subjects being enrolled into the amended protocol.

Promedior may make administrative changes (i.e., changes that do not significantly affect subject safety or the study's scope or scientific quality) without any further approvals.

9.5. Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and other study personnel must not disclose such information without prior written approval from Promedior.

Subject confidentiality will be strictly maintained to the extent possible under the law. Subject names must not be disclosed. Subjects will be identified in the eCRFs and other documents submitted to Promedior or its designated representative, by their initials, birth date, and/or assigned subject number. Documents that identify the subject (e.g., the signed ICF) should not to be submitted to Promedior or its designated representative, and must be maintained in confidence by the Investigator.

9.6. Publication Policy

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee comprised of Investigators participating in the study and representatives from Promedior, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor.

10. STUDY MANAGEMENT

10.1. Case Report Forms and Source Documentation

The Sponsor or designee will provide the study centers with eCRFs for each subject.

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. An explanation should be given for all missing data.

The Investigator must electronically sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

10.2. Monitoring

During the course of the study, the CRA will make study center visits to review protocol compliance, compare eCRFs and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements in respect to Good Clinical Practice. eCRFs will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

10.3. Inspections

Regulatory authorities and/or quality assurance personnel from Promedior or its designated representative may wish to carry out such source data checks and/or in-center audit inspections. The investigator assures Promedior of the necessary support at all times. In the event of an audit, the Investigator agrees to allow the Sponsor's representatives and any regulatory agencies access to all study records.

10.4. Financial Disclosure Reporting Obligations

Investigators and Sub-investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its regulatory obligation. Investigators and Sub-investigators must commit to promptly updating the information if any relevant changes occur during the study and for a period of one year after the completion of the study.

10.5. Archiving Study Records

Essential documents should be retained for a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

However, these documents should be retained for a longer period if required by the applicable local requirements.

ICH requires that subject identification codes be retained for at least 15 years after the completion or discontinuation of the study.

11. REFERENCES

ATS (2002). "ATS Statement: Guidelines for the Six-Minute Walk Test." AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE **166**: 111-117.

Birring, S. S., B. Prudon, et al. (2003). "Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ)." Thorax **58**(4): 339-343.

Collard, H. R., B. B. Moore, et al. (2007). "Acute exacerbations of idiopathic pulmonary fibrosis." Am J Respir Crit Care Med **176**(7): 636-43.

Collard, H. R., E. Yow, et al. (2013). "Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials." Respiratory Research **14:73**.

Fernandez Perez, E. R., C. E. Daniels, et al. (2010). "Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study." Chest **137**(1): 129-37.

Frankel, S. K. and M. I. Schwarz (2009). "Update in idiopathic pulmonary fibrosis." Curr Opin Pulm Med **15**(5): 463-9.

Gillmore, J. D., W. L. Hutchinson, et al. (2004). "Autoimmunity and glomerulonephritis in mice with targeted deletion of the serum amyloid P component gene: SAP deficiency or strain combination?" Immunology **112**(2): 255-264.

Gomer, R. H. and M. L. Lupher, Jr. (2010). "Investigational approaches to therapies for idiopathic pulmonary fibrosis." Expert Opin Investig Drugs **19**(6): 737-45.

Haudek, S. B., Y. Xia, et al. (2006). "Bone marrow-derived fibroblast precursors mediate ischemic cardiomyopathy in mice." Proc Natl Acad Sci U S A **103**(48): 18284-9.

Hawkins, P. N., R. Wootton, et al. (1990). "Metabolic studies of radioiodinated serum amyloid P component in normal subjects and patients with systemic amyloidosis." J Clin Invest **86**(6): 1862-9.

King, T. E., W. Z. Bradford, et al. "A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis." New England Journal of Medicine **370**(22): 2083-2092.

Lupher, M. L., Jr. and W. M. Gallatin (2006). "Regulation of fibrosis by the immune system." Adv Immunol **89**: 245-88.

MacIntyre, N., R. O. Crapo, et al. (2005). "Standardisation of the single-breath determination of carbon monoxide uptake in the lung." European Respiratory Journal **26**(4): 720-735.

Maldonado, F., T. Moua, et al. "Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis." European Respiratory Journal **43**(1): 204-212.

Meltzer, E. B. and P. W. Noble (2008). "Idiopathic pulmonary fibrosis." Orphanet J Rare Dis **3**: 8.

Miller, M. R., R. Crapo, et al. (2005a). "General considerations for lung function testing." Eur Respir J **26**: 153-161.

Moeller, A., S. E. Gilpin, et al. (2009). "Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis." Am J Respir Crit Care Med **179**(7): 588-94.

Murray, L. A., Q. Chen, et al. (2011). "TGF-beta driven lung fibrosis is macrophage dependent and blocked by Serum amyloid P." Int J Biochem Cell Biol **43**(1): 154-162.

Nalysnyk, L., J. Cid-Ruzafa, et al. (2012). "Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature." European Respiratory Review **21**(126): 355-361.

Navaratnam, V., K. M. Fleming, et al. (2011). "The rising incidence of idiopathic pulmonary fibrosis in the U.K." Thorax **66**(6): 462-7.

Patel, A. S., R. J. Siegert, et al. "The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire." Thorax. 2012 Sep;67(9):804-10. doi: 10.1136/thoraxjnl-2012-201581. Epub 2012 May 3.

Pilling, D., C. D. Buckley, et al. (2003). "Inhibition of fibrocyte differentiation by serum amyloid P." J Immunol **171**(10): 5537-46.

Pilling, D., D. Roife, et al. (2007). "Reduction of bleomycin-induced pulmonary fibrosis by serum amyloid P." J Immunol **179**(6): 4035-44.

Raghu, G., H. R. Collard, et al. (2011). "An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management." Am J Respir Crit Care Med **183**(6): 788-824.

Raghu, G., D. Weycker, et al. (2006). "Incidence and prevalence of idiopathic pulmonary fibrosis." Am J Respir Crit Care Med **174**(7): 810-6.

Raghunath, S. (2014). "Quantitative Stratification of Diffuse Parenchymal Lung Diseases " PLoS Med **9**(3).

Richeldi, L., R. M. du Bois, et al. "Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis." New England Journal of Medicine **370**(22): 2071-2082.

Verstovsek, S., R. A. Mesa, et al. (2012). "A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis." N Engl J Med **366**(9): 799-807.

Wanger, J., J. L. Clausen, et al. (2005). "Standardisation of the measurement of lung volumes." Eur Respir J **26**(3): 511-522.

Zavaletta, V. A., B. J. Bartholmai, et al. "High Resolution Multidetector CT-Aided Tissue Analysis and Quantification of Lung Fibrosis." Academic Radiology **14**(7): 772-787.

12. APPENDIX A SCHEDULE OF EVENTS

		Week 0 (+/-1day)		**W4, W8, W12, W16, W20,W24 (+/- 3d)**	**W28/ EOS (+/- 3d)**	**W28 (+/- 3d)**		**W32 (+/- 3d)**	**W36 (+/- 3d)**	**W40 (+/- 3d)**	**W44 (+/- 3d)**	**W48 (+/- 3d)**	**W52 (+/- 3d)**	**Week 56 (+/-3days)**	
		Baseline Dosing Day 1	**Dosing Days 3, 5**	**Dosing Day 1**		**Dosing Day 1**	**Dosing Days 3, 5**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Baseline Dosing Day 1**	**Dosing Days 3, 5**
Informed Consent	x														
Demographics	x														
Past Medical History	x														
Inclusion/Exclusion	x	x													
Vital Signs (pre and post dose and every 15 minutes for the duration of the infusion	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Exam[1]	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Height (cm)	x														
Weight (kg)	x	x		x		x	x	x	x	x	x	x	x	x	
Prior/Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Special list of excluded medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AE/SAE Assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG & Cytokines (ONLY in the event of an IRR after Baseline)		x	x	x			x	x	x	x	x	x	x	x	x
Efficacy Assessment[2]															
Patient Reported Outcomes; K-BILD & LCQ	x	x		x	x	x		x	x	x	x	x	x		

Pulmonary Function Tests (PFTs)	x	x		x	x	x		x	x	x	x	x	x		
DLCO[3]	x	x			x	x									
FRC &TLC by nitrogen washout method[4]	x	x			x	x									
HRCT (with spirometry at select sites)[5]		x			x	x									
6-minute walk test	x	x		x	x	x		x	x	x	x	x	x		
Pregnancy test Each visit after V4 for all WOCBP	x														
Complete Blood Count	x	x		x	x	x				x			x		
Chemistry, BUN/creatinine	x	x		x	x	x				x			x		
Coagulation	x	x		x	x	x				x			x		
Status of baseline genetic characteristics[6]		x													
Anti-pentraxin 2 antibodies (ADA), Pre-dose		x		x	x	x				x			x		
Pentraxin-2 levels, Pre-dose		x		x	x	x				x			x		
Exploratory laboratory assessments (optional)[7]		x			x	x									
PRM-151 dosing[8]		x	x	x		x	x	x	x	x	x	x	x	x	x

		W60 (+/- 3d)	**W64 (+/- 3d)**	**W68 (+/- 3d)**	**W72 (+/- 3d)**	**W76 (+/- 3d)**	**W80 (+/- 3d)**	**Week 84 (+/-3days)**		**W88 (+/- 3d)**	**W92 (+/- 3d)**	**W96 (+/- 3d)**	**W100 (+/- 3d)**	**W104 (+/- 3d)**	**W108 (+/- 3d)**	
		Dosing Day 1	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Baseline Dosing Day 1**	**Dosing Days 3, 5**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Dosing Day 1**	**Baseli Dosi Day**
Informed Consent	x															
Demographics	x															
Past Medical History	x															
Inclusion/Exclusion	x															
Vital Signs (pre and post dose and every 15 minutes for the duration of the infusion	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Exam[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height (cm)	x															
Weight (kg)	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x
Prior/Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Special list of excluded medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AE/SAE Assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG & Cytokines (ONLY in the event of an IRR after Baseline)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Efficacy Assessment[2]																
Patient Reported Outcomes; K-BILD & LCQ	x		x			x				x			x			x

Pulmonary Function Tests (PFTs)	x		x			x				x			x			x
DLCO[3]	x					x										
FRC &TLC by nitrogen washout method[4]	x					x										
HRCT (with spirometry at select sites)[5]						x										
6-minute walk test	x		x			x				x			x			x
Pregnancy test Each visit after V4 for all WOCBP	x															
Complete Blood Count	x		x			x				x			x			x
Chemistry, BUN/creatinine	x		x			x				x			x			x
Coagulation	x		x			x				x			x			x
Status of baseline genetic characteristics[6]																
Anti-pentraxin 2 antibodies (ADA), Pre-dose			x			x				x			x			x
Pentraxin-2 levels, Pre-dose			x			x				x			x			x
Exploratory laboratory assessments (optional)[7]																
PRM-151 dosing[8]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[1] Full physical exam at screening and an abbreviated physical exam thereafter.
[2] [redacted]
[8] Dosing on Days 1, 3, and 5 will be repeated every 28 weeks during the extension study. If the subject is not able to adhere to the original dosing schedule, the subject should be dosed as soon as possible within 2 weeks of the scheduled visit. If the subject dosing is >2 weeks sponsor should be consulted.

13. APPENDIX B SIX-MINUTE WALK TEST

TECHNICAL ASPECTS OF THE 6MWT
(ATS 2002)

Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.

3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.
4. Pulseoximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable. The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The SpO2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO2. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulseoximeters have considerable motion artifact that prevents accurate readings during the walk.
5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (see APPENDIX E for the Borg scale and instructions).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

   You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

   Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

   "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

   Start now or whenever you are ready."

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark

the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stop- watch at a race. After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go." When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go." When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done." When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only2 minutes left." When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping pre- maturely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

10. Post-test: Record the post walk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

APPENDIX WORKSHEET

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _____ _____ _____

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____meters

Weight: _____lbs, _____kg Blood pressure: _____/ _____ Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____L/min, type _____

	Baseline	End of Test
Time	___:___	___:___
Heart Rate	_____	_____
Dyspnea	____	____(Borg scale)
Fatigue	____	____(Borg scale)
SpO_2	____%	____%

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ____(X60 meters) + final partial lap: _____meters =

Total distance walked in 6 minutes: _____meters

Predicted distance: _____meters Percent predicted: _____%

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

Note: start and stop time collection is not required

14. APPENDIX C BORG SCALE

Borg Scale for Rating Dyspnea and Overall Fatigue (ATS 2002)

Score	Definition
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	10Very, very severe (maximal)

15. APPENDIX D THE KING'S BRIEF INTERSTITIAL LUNG DISEASE QUESTIONNAIRE (K-BILD)

(Patel, Siegert et al.)

The King's Brief Interstitial Lung Disease Questionnaire (K-BILD)©2011

This questionnaire is designed to assess the impact of your lung disease on various aspects of your life. Please circle the response that best applies to you for each question

1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill.						
1. Every time	2. Most times	3. Several Times	4. Some times	5. Occasionally	6. Rarely	7. Never
2. In the last 2 weeks, because of my lung condition, my chest has felt tight.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
3. In the last 2 weeks have you worried about the seriousness of your lung complaint?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
4. In the last 2 weeks have you avoided doing things that make you breathless?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
5. In the last 2 weeks have you felt in control of your lung condition?						
1. None of the time	2. Hardly any of the time	3. A little of the time	4. Some of the time	5. A good bit of the time	6. Most of the time	7. All of the time
6. In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
8. In the last 2 weeks, my lung condition has made me feel anxious.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
10. In the last 2 weeks, how much of the time have you felt your lung disease is getting worse?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
12. In the last 2 weeks have you expected your lung complaint to get worse?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
14. In the last 2 weeks, has your lung condition made you think more about the end of your life?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
15. Are you financially worse off because of your lung condition?						
1. A significant amount	2. A large amount	3. A considerable amount	4.A reasonable amount	5. A small amount	6. Hardly at all	7. Not at all

16. APPENDIX E SUMMARY OF CHANGES

Changes from Version 3.0 to Version 4.0

Section(s)	Change
Inclusion	As there is no information available at the moment on the effect of PRM-151 on sperm and your partner might become pregnant you must use effective methods forms of contraception during this study. Effective methods of birth control include the use of oral contraceptives or Depo-Provera, with an additional barrier method (diaphragm with spermicidal gel or condoms with spermicide), double barrier methods (diaphragm with spermicidal gel and condoms with spermicide), partner vasectomy and total abstinence (only if total abstinence is the preferred method and usual lifestyle of the subject). Adequate contraceptive use should be continued until 28 days after the final dose of the study drug. Clarified WOCBP birth control.
Inclusion	Added: Subject and the treating physician considered all medicinal treatment options and / or possibly a lung transplantation prior to considering participation in the study.
Efficacy Assessments/Schedule of Events	Added: ECG and Cytokines completed at baseline, prior to PRM-151 dosing. ECG and cytokines will only be repeated then in the event of an infusion-related reaction (IRR) afterBaseline.
Schedule Of Events	Added note for pre and post vitals collection
Throughout	Formatting updates and minor corrections/clarifications to text to harmonize with PRM-151-101
Infusion Reaction	Changed: Infuse over 1 hour to infuse over 120 minutes

Changes from Version 2.0 to Version 3.0

Section(s)	Change
7.10.3	Removed the requirement to obtain a spirometry guided HRCT at full expiration (FRC)
Throughout	Formatting updates and minor corrections/clarifications to text.

Changes from Version 1.0 to Version 2.0

Section(s)	**Change**
Cover page	Added Amendment 1 version information.
Study Title	Modified title of the protocol from "Pilot Trial" to "A Phase 2 Trial".
Synopsis: (Primary Objective); 2.1	Modified the Primary Objective from "demonstrating the superiority" to "determining the effect size of change". Clarified that the changes will be in normal lung "parenchyma". Updated "by structural" to "on high-resolution CT". Added subject can be on a dose of nintedanib.
Synopsis: (Secondary Objective(s); 2.2	Modified from "demonstrating superiority" to "determine effect size" and from "preservation or increase" to "change". Clarified that change in normal lung "parenchyma" will be quantified "on high-resolution CT (HRCT) imaging analysis, pooling subjects on a stable dose of pirfenidone with subjects not on other treatment for IPF". Modified the duration of treatment subjects will be assessed for tolerability and safety from "24 weeks" to "28 weeks". Added subject can be on a dose of nintedanib. Modified an assessment of "6 minute walk distance" to "gas exchange (DLCO)". Added Secondary Objectives: • Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone and separately in subjects not on other treatments for IPF. • Determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on HRCT imaging analysis, separately in subjects on a stable dose of pirfenidone and in subjects not on other treatments for IPF. • Determine the effect of PRM-151 on pulmonary function in addition to mean change in FVC% predicted. • Determine the effect size of PRM-151 relative to placebo on 6 minute walk distance.

Section(s)	Change
Synopsis: (Exploratory Objective(s); 2.3	Removed Exploratory Objectives: • Assess the ability of PRM-151 to preserve or increase gas exchange • Assess the impact of PRM-151 on functional respiratory imaging parameters Added Exploratory Objective: • Evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC % predicted and 6 minute walking distance, pooling subjects on a stable dose of pirfenidone with subjects not on other treatment for IPF, and separately in subjects on a stable dose of pirfenidone and in subjects not on other treatments for IPF Added subject can be on a dose of nintedanib.
Synopsis: (Study Endpoints) Secondary: Structural Imaging; 2.2	Clarified total lung measurements using HRCT (in ml and % of total lung volume) using quantitative imaging software. Modified "Transitions between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and mild low attenuation areas) by quantitative imaging software." to "Mean change from Baseline to Week 28 in volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of normal lung (non-ILA), including normal and mild low attenuation areas, using quantitative imaging software." Added Secondary Endpoint: • Correlation between mean change from Baseline to Week 28 in FVC % predicted and mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA), including ground glass density, reticular changes, and honeycombing by quantitative imaging software.
Synopsis: (Study Endpoints) Secondary: Safety; 2.2	Modified the duration of assessment of tolerability and safety from "24 weeks" to "28 weeks".
Synopsis: (Study Endpoints) Secondary: Disease related events associated with mortality. 2.2; 7.12.1.1	Modified the duration of assessment from "24 weeks" to "28 weeks". Modified the definition of respiratory decline based on the definitions of IPF-related acute exacerbation proposed by an expert committee sponsored by the Clinical Research Network and the National Heart Lung and Blood Institute (NHLBI).

Section(s)	Change
Synopsis: (Study Endpoints) Secondary: Pulmonary Function Tests; 2.2	Removed PFTs: • Time-weighted average (TWA) of change in FVC% predicted from Baseline to Week 28. • TWA of change in FVC in ml from Baseline to Week 28. Added PFTs: • Proportion of subjects with stable disease by FVC %, defined as a change in FVC % predicted of <5% from Baseline to Week 28. • Proportion of subjects with stable disease by absolute FVC, defined as a change in FVC of < 100ml from Baseline to Week 28.
Synopsis: (Study Endpoints) Secondary: Exploratory; 2.3	Added Other Weeks • Examine the change from baseline at Weeks 4, 8, 12, 16, 20, and 24 for the FVC % predicted, FVC (l), and 6MWT distance Added Structural Imaging • Transitions from Baseline to Week 28 between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and mild, moderate, and severe low attenuation areas) by quantitative imaging software. • Correlation of transitions between categories of lung features by quantitative imaging and changes in FVC% predicted. • Correlation of transitions between categories of lung features by quantitative imaging and changes in DLCO. • Impact of inspiratory effort on results of HRCT quantitative imaging. Removed Quantitative Functional Respiratory Imaging • Change from baseline to 28 weeks in regional lung volumes, specific airway volumes and resistance as measured by quantitative imaging software (FluidDA).
Synopsis: Study Design; 4.1	Clarification on randomization 2:1 ratio. The randomization will be stratified according to other treatments for IPF (subjects receiving pirfenidone and subjects with no other treatment for IPF). Modified the evaluation of the Total Lung Capacity by "Helium dilution method (TLC by He)," to "Nitrogen washout method". Modified the number of subjects enrolled from "60" to "117". Added dosing on Days 1, 3 and 5 will be repeated once every 24 weeks for the open label study extension. Added subject can be on a dose of nintedanib.
Synopsis: Study Inclusion Criteria; 5.1.1	Removed "post-bronchodilator" from Inclusion Criteria 8. Added subject can be on a dose of nintedanib.

Section(s)	Change
Synopsis: Study Exclusion Criteria; 5.1.1	Removed Exclusion Criteria 8. Subjects has received nintedanib within the 4 weeks before baseline.
Synopsis: Efficacy Assessments; 4.1.3	Modified from "Order of Events" to "Schedule of Events". Modified pulmonary function from "TLC by helium dilution" to "TLC by nitrogen washout". Clarified that HRCT will be performed with spirometry at selected sites. Added dosing on Days 1, 3 and 5 will be repeated once every 24 weeks for the open label study extension.
Synopsis: Safety Assessments	Added "Safety will be evaluated from reported adverse events (AEs), scheduled physical examinations, vital signs, and clinical laboratory test results."
Synopsis: Statistical Methods:	Clarified the analysis plan for the study.
Synopsis: Sample Size Considerations; 8.1	Clarified the sample size calculations and provided rationalization based on updated subject enrollment numbers. Added that the randomization system will ensure that at least 25% of the subjects in the final study population are on no other therapy for IPF at baseline.
List of Abbreviations	Added: ADA, AESI, ILA, ILD, and LAA
1.	Modified the title from "Introduction" to "Introduction and Study Rational"
1.3.1	Modified the title from "Imbio" to "Imbio Lung Texture Analysis" Clarified the use of Imbio Lung Texture Analysis and how it will be used for analysis in the study.
1.3.2	Clarified the retrospective quantitative imaging analysis of PRM-151 data in Study PRM151f-12GL.
1.5	Added rational for using HRCT and explanation of the low risk of radiation to the subjects.
4.1.1	Clarified the duration of assessments are to occur weeks, 4, 8, 12, 16, 20, 24 and 28 weeks for efficacy and safety

Section(s)	Change
5.1.2	Updated Exclusion Criteria 10. to be consistent with the Synopsis. Subjects that are unable to refrain from use of the following: • Short acting bronchodilators on the day of and within 12 hours of pulmonary function, DL_{CO}, and 6 minute walk assessments. • Long acting bronchodilators on the day of and within 24 hours of these assessments.
5.7	Modified the procedure for the Data Monitoring Committee. The DMC to review the safety data in a blinded manner, but a procedure will be in place to allow the committee an immediate unblinding of either specific cases or of the whole study in case of detection of a potential safety signal necessitating an unblinded review of some (or all) subjects.
6.2; 7.12.1.2; Appendix A	Clarified that if a subject experiences an infusion related reaction, an ECG and a blood sample for cytokines should be collected as soon as possible after stabilization of the subject.
6.8	Clarified rational for dose selection based on data collected on subjects with myelofibrosis treated with PRM-151.
7.9	Added subject can be on a dose of nintedanib. Clarified that subjects currently on a stable dose of pirfenidone or nintedanib they are allowed to stop taking pirfenidone or nintedanib while remaining in the study but they are not allowed to start dosing with the other.
7.10.1	Modified lung volumes to be done with "Nitrogen washout method" and removed "according to ATS guidelines".
7.10.2	Clarified that the 6MWT should be the last efficacy assessment completed, by the subject. If it is not possible to complete the 6MWT last, then allow a 30 minute recovery time before continuing with the next efficacy assessment
7.10.4	Clarified that if possible, the questionnaires should be the first assessments completed by the subjects.
7.12.1; 7.12.2	Clarified when AEs should be recorded.
7.12.4	Updated the contact information for reporting Serious Adverse Events
7.12.4.1	Updated the information for reporting Adverse Events for Special Interest
7.12.4.5	Added information regarding reporting pregnancies.
8.2, 8.3, 8.4, 8.5	Updated the General Considerations of Statistical Analysis, Protocol Deviations, Analysis Datasets, Planned Statistical Analyses section in the protocol.

Section(s)	Change
9.	Updated Section numbers for Ethical, Legal, and Administrative Considerations. From Section 8.4 to Section 9.
References	Two new references were added.
Appendix A	Added a footnote to clarify the dosing on Days 1, 3 and 5 will be repeated once every 24 weeks for the open label study extension.
Appendix B, C and G	Removed Appendix B; Pulmonary Function Tests, Appendix C; Diffusion Capacity and Appendix G; Common Terminology Criteria for Adverse Events
Throughout	Formatting updates and minor corrections/clarifications to text.

17. APPENDIX F: NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE)

The United States of America (USA) National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v.4.0) can be found on the following website.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
[Accessed: 13 February 2013]

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 v4.0 includes 764 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. MedDRA v12.0.

18. G. APPENDIX LEICESTER COUGH QUESTIONNAIRE (LCQ)

(Birring, Prudon et al. 2003)

APPENDIX 1: Leicester Cough Questionnaire. © 2001

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Some times	Occasionally	Rarely	Never

3. In the last 2 weeks, have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

6. In the last 2 weeks, my cough has made me feel anxious

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

10. In the last 2 weeks, has your cough disturbed your sleep?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

11. In the last 2 weeks, how many times a day have you had coughing bouts?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Some times during the day	Occasionally through the day	Rarely	None

12. In the last 2 weeks, my cough has made me feel frustrated

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

13. In the last 2 weeks, my cough has made me feel fed up

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

15. In the last 2 weeks, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

16. In the last 2 weeks, have you worried that your cough may indicate serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Some times when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

Signatures

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Date 20 DEC 2016

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Date

Statistical Analysis Plan

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

PRM-151-202

Versions History

Version Number	Date	Detail
Version 1	20 Dec 2016	Not applicable: First version

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Contents

Abbreviations and definitions

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis Of Variance
AST	Aspartate aminotransferase
ATS	All Treated Set
BMI	Body Mass Index
CRO	Contract Research Organization
CS	Clinically Significant
CT	Computed Tomography
DLCO	Diffusing capacity of the Lung for Carbon monoxide (CO)
DMC	Data Monitoring Committee
EO	Exploratory Objective
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
HRCT	High-Resolution Computed Tomography
ICH	International conference of harmonization
ILA	Interstitial Lung Abnormality
IMP	Investigational Medical Product
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IV	Intravenous
K-BILD	King's Brief Interstitial Lung Disease Questionnaire
LCQ	Leicester Cough Questionnaire
LLN	Lower Limit Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Non-Clinically Significant
NHLBI	National Heart Lung and Blood Institute
PFT	Pulmonary Function Test
PO	Primary Objective
PP	Per-Protocol
PRO	Patient Reported Outcome

PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SO	Secondary Objective
SOC	System Organ Class
SVC	Slow Vital Capacity
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TLC	Total Lung Capacity
ULN	Upper Limit Normal
US	United States

1 Introduction

This document is the statistical analysis plan (SAP) for the PRM-151-202 study. The purpose of this SAP is to provide a comprehensive and detailed description of the statistical analyses that will be carried out to assess the clinical efficacy and safety of the study treatment, as outlined in the study protocol version 4.0, dated 4 February 2016. The SAP pre-specifies the statistical approaches to be used and is validated prior to the study database lock and the unblinding of the randomisation schedule, to ensure the credibility of the study findings.

2 Highlights from study protocol

2.1 Background/Rationale

Full details of the background and rationale for the study are provided in Section 1 of the protocol.

2.2 Study Objectives

2.2.1 Primary objective (PO)

The primary objective of this study (**PO1**) is to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC [% predicted], pooling subjects on a stable dose of pirfenidone or nintedanib and subjects not on other treatment for IPF.

2.2.2 Secondary objectives (SO)

The secondary objectives of this study are:

- **SO1:** To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on high-resolution CT (HRCT) imaging analysis, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF.
- **SO2:** To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC [% predicted], separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- **SO3:** To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on HRCT imaging analysis, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- **SO4:** To assess the tolerability and safety of PRM-151 in subjects with IPF through Week 28.
- **SO5:** To assess the ability of PRM-151 to reduce disease-related events associated with mortality

- **SO6:** To determine the effect size of PRM-151 relative to placebo on pulmonary function in addition to mean change in FVC [% predicted]
- **SO7:** To determine the effect size of PRM-151 relative to placebo on 6 minute walk distance
- **SO8:** To determine the effect size of PRM-151 relative to placebo on DLCO.

2.2.3 Exploratory Objectives (EO)

The exploratory objectives of this study are:

- **EO1:** To evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC [% predicted] and 6 minute walking distance, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF and separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- **EO2:** To assess the impact of PRM-151 on disease related symptoms.
- **EO3:** To assess the impact of PRM-151, disease pathogenesis and disease progression on exploratory serum, cellular and genetic biomarkers
- **E04:** to explore the relationship between PK and select PD parameters

2.3 Investigational plan

2.3.1 Study design and randomisation

This study is a Phase 2, randomized, double-blind, placebo controlled, pilot study designed to evaluate the efficacy and safety of PRM-151 administered through Week 24 to subjects with IPF. Subjects meeting the eligibility criteria for the study will be randomized with a 2:1 ratio to PRM-151 at a dose of 10 mg/kg every 4 weeks or placebo. The randomization will be stratified according to other treatments for IPF (with two strata: patients receiving either pirfenidone or nintedanib and patients with no other treatment for IPF, with a minimum of 25% of patients on no other treatment). Efficacy will be evaluated through pulmonary function tests (PFTs) including spirometry, Diffusion Capacity (DLCO) and Total Lung Capacity by Nitrogen washout method (TLC), quantitative imaging analysis of high resolution CT (HRCT), 6 minute walk test (6MWT), and patient reported outcomes (PROs).

Subjects will be evaluated for study eligibility during Screening within 4 weeks before enrollment and baseline assessments. Subjects who are determined to be eligible, based on screening assessments, will be enrolled in the study and randomly allocated to treatment with PRM-151 or placebo. Subjects will receive study drug treatment for at least 24 weeks.

Approximately 117 subjects will be randomly assigned on a 2:1 basis to treatment with PRM-151 or placebo, as follows:

- PRM-151 10 mg/kg IV infusion over 60 minutes days 1, 3, and 5 of week 0, then one infusion every 4 weeks

- Placebo IV infusion over 60 minutes on days 1, 3, and 5 of week 0, then one infusion every 4 weeks

After completion of study treatment through Week 24, all subjects may receive PRM-151 10 mg/kg IV infusion over 60 minutes Days 1, 3, and 5, then once every 4 weeks for up to an additional 96 weeks in an open label study extension. Dosing on Days 1, 3 and 5 will be repeated once every 24 weeks.

2.3.2 Determination of sample size

The primary objective is not to formally demonstrate the superiority of PRM-151 over placebo, but to provide a reliable estimate of the size of the effect of PRM-151 on absolute change from baseline to 28 weeks in mean FVC [% predicted], hereafter referred to as the primary endpoint. Nevertheless, the sample-size has been calculated to ensure a sufficient power to demonstrate the efficacy of PRM-151 over placebo on the primary endpoint under a set of hypotheses on effect sizes in the two groups and on the variability of the primary endpoint. The primary endpoint will be tested in a model with two types of subjects: subjects on a stable dose of pirfenidone or nintedanib, and subjects not on other treatment for IPF. The sample size calculation is based on the following assumptions:

- Primary endpoint is normally distributed.
- Homogeneity of variance, *i.e.*, the standard deviation is the same in both arms, and for both types of subjects.
- Randomization ratio PRM-151: placebo equals 2:1.
- Expected value of the primary endpoint for subjects on pirfenidone or nintedanib will be -1.5%.
- Expected value of the primary endpoint for subjects on no other treatment will be -3%.
- Expected value of the primary endpoint for subjects on PRM-151 will be $\geq$ 0.75%.
- Standard deviation of the primary endpoint is 5%.
- 75% of subjects will be on a stable dose of pirfenidone or nintedanib.
- 25% of subjects will not be on other treatment for IPF.
- Significance level (α)=0.10 two-sided.
- Desired power to demonstrate superiority is 80%.

A sample size of one hundred and two (102) evaluable subjects in total (68 PRM-151 and 34 placebo) is enough to demonstrate statistical significance at $p<0.10$ two-sided with a power of 80% under the above assumptions. Assuming a non-evaluability rate of about 15%, 117 subjects in total (78 PRM-151 and 39 placebo) are to be enrolled. Stratified randomization will ensure a balance of PRM-151: placebo within patients on pirfenidone or nintedanib and not on any other therapy, with at least 25% of patients on no other therapy.

2.3.3 Study assessments and study plan

Efficacy Assessments

Subjects undergo testing on an every 4 week basis after randomization (occurring at weeks 4, 8, 12, 16, 20, 24 and 28) for efficacy and safety (See Figure 1). For all analysis presented in this SAP we considered W28 as the end of study date. During treatment, PFTs, 6MWT, and PROs will be evaluated on an every 4 week basis. HRCT will be performed on Day 1 as the Baseline assessment and again at the completion of treatment at Week 28. HRCT and PFTs must be done on the same day. PFTs will be reviewed centrally by reviewers blinded to treatment group and time point. This central evaluation of PFTs will be used for the primary analysis of the study.

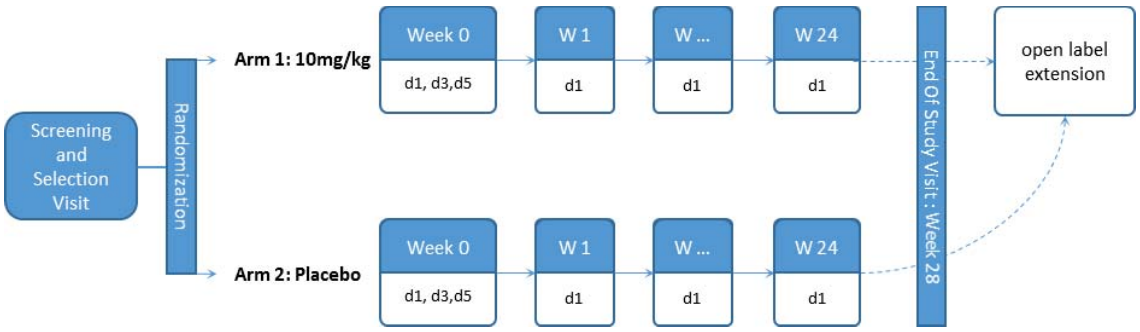

Figure 1: Study Plan

Tolerability/Safety Assessments

Tolerability/Safety will be evaluated over the treatment period (up to week 28) from reported adverse events (AEs), scheduled physical examinations, vital signs, and clinical laboratory test results. Adverse events and concomitant medications will be assessed at all study visits. In addition, information regarding hospitalizations, emergency department visits, and unscheduled or urgent care visits to a health care provider due to a deterioration in respiratory status or symptoms will be collected at all study visits.

Schedule of events

Redacted 271217

3 Analysis datasets

3.1 Reasons for excluding patients from analysis datasets

3.1.1 Major protocol deviations

Major protocol deviations are defined as deviations liable to prevent or change the interpretation of the results of the primary efficacy analysis of the study. Thus, a Study Deviation Guidance Document has been prepared (Final version, dated 27July, 2016). Tthis guidance is not exhaustive and will be reviewed at the time of the blind review meeting.

3.1.2 Minor protocol deviations

All deviations will be reviewed and adjudicated as either major or minor during the blind review meeting before database lock and unblinding of the study drug treatment code.

3.1.3 Study treatment discontinuations - Study discontinuations

The Investigator may discontinue study drug treatment prematurely for any of the following reasons:

- Subject, Investigator, or Sponsor request
- Protocol violation
- AE
- Pregnancy
- Progression of disease that, in the opinion of the Investigator, precludes further study drug treatment
- Subject decision: a subject may withdraw consent to participate in the study at any time

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol.

All subjects are required to adhere to the protocol-specified visit schedule. If a subject misses a scheduled visit, attempts should be made to reschedule the visit within the visit windows described above. Failure to attend scheduled study visits may result in discontinuation from the study.

3.2 Primary efficacy dataset: All Treated Set (ATS)

The All Treated Set (ATS) will consists in all randomized patients having received at least one administration of the study medication. The patients will be analyzed in the treatment arm attributed by the randomization process whatever the treatment they actually received ("as randomized" analysis).

The ATS dataset will be used for the for the primary efficacy analyses in this trial.

3.3 Per-protocol (PP) dataset

The Per Protocol (PP) set will comprise of a subset of the ATS analysis population:

- Randomized
- treated with the IMP,
- having received the planned IMP infusions at least for the complete three first cycles
- who did not present any major protocol deviations.
- who have at least one post-cycle 3 evaluation of the primary efficacy criterion (FVC [% predicted])

The PP dataset will be used for secondary analyses of the primary efficacy criterion and for the analysis of some selected secondary efficacy criteria, as described in section 5.2.5.2.

3.4 Safety (SAF) dataset

The safety dataset is defined as all randomized subjects having received at least one dose of study treatment. In the event of subjects having received treatments that differed from those assigned according to the randomisation schedule, then the safety analyses should be conducted according to the treatment actually received (As Treated analysis) rather than according to the randomisation groups.

The SAF dataset will be used to perform the analysis of safety.

4 Endpoints for analysis

4.1 Efficacy endpoints

4.1.1 Primary efficacy endpoint

The primary efficacy endpoint for the study is the mean change from baseline in FVC [% predicted] from Baseline to Week 28. Data for FVC [% predicted] will be provided by BioMedical Systems (BMS) and analysed without any transformation or derivation. The specification on how this variable is measured and computed are provided in the BMS specification document (PRM 151-202 Analysis Plan FINAL Version 1.0 02MAY16).

4.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints for the study are:

- Structural Imaging:
  - Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA) including ground glass density, reticular changes, and honeycombing, using quantitative imaging software.
  - Mean change from Baseline to Week 28 in volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of normal lung (non-ILA), including normal and mild low attenuation areas, using quantitative imaging software.
  - Correlation between mean change from Baseline to Week 28 in FVC [% predicted] and mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA), including ground glass density, reticular changes, and honeycombing by quantitative imaging software.
- FVC [ml and % predicted] based pulmonary function tests:
  - Proportion (%) of subjects with a decline in FVC [% predicted] of ≥ 5% and ≥ 10% from baseline to week 28.
  - Proportion (%) of subjects with a decline in FVC [ml] of ≥ 100ml and ≥ 200ml from baseline to week 28.
  - Proportion of subjects with an increase in FVC [% predicted] of ≥ 5% and ≥10% from baseline to week 28.
  - Proportion of subjects with an increase in FVC [ml] of ≥ 100 ml and ≥ 200 ml from baseline to week 28.
  - Proportion of subjects with stable disease by FVC [% predicted], defined as a change in FVC [% predicted] of < 5% from baseline to week 28.
  - Proportion of subjects with stable disease by FVC in ml, defined as a change in FVC of < 100ml from Baseline to week 28.
- Others pulmonary function tests:

  - Mean change from Baseline to Week 28 in Hb-corrected DLCO *i.e.*, diffusion capacity of carbon monoxide [% predicted].
- Other endpoints
  - Change in 6-minute walk distance [m] from baseline to week 28.

4.1.3 Exploratory efficacy endpoints

There are five types of exploratory endpoints for the study. The first type is based on the examination of FVC [% predicted] for **other weeks**:

- Change from Baseline at Weeks 4, 8, 12, 16, 20, 24 and 28 for the FVC [% predicted], FVC [ml], and 6MWT distance [m].

The second type of exploratory endpoints is based on **structural imaging**:

- Transitions from Baseline to Week 28 between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and mild, moderate, and severe low attenuation areas) by quantitative imaging software.
- Correlation of transitions between categories of lung features by quantitative imaging and changes in FVC [% predicted].
- Correlation of transitions between categories of lung features by quantitative imaging and changes in DLCO.
- Correlation between total lung volume by nitrogen washout and total lung volume by imaging
- Correlation of changes in interstitial lung abnormalities and PROs and 6MWD
- Impact of inspiratory effort on results of HRCT quantitative imaging.
- Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume), representative of interstitial lung abnormalities (ILA) in patients with SVC breathhold at CT scanning ≥90% of SVC supine (comparing PRM151 vs placebo)

The Third group of exploratory endpoint is based on **patient reported outcomes**:

- Change in Patient Reported Outcomes as measured by
  - King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and
  - Leicester Cough Questionnaire (LCQ) from Baseline to Week 28.

The fourth group of exploratory endpoint is based project investigator assessed outcome :

- Acute exacerbations and time to first reported acute exacerbation

The last type of exploratory endpoints is related to the analysis of **biomarkers**:

- Changes in serum and cellular biomarkers and response according to baseline genetic characteristics: including but not limited to TLR3, L412F polymorphism, and MUC5B promoter polymorphism. This analysis may be provided at a later stage than the rest of the analyses, some or all the corresponding data may not be available at the time of the database lock.

Pharmacokinetic endpoints: Pentraxin levels will be assayed at baseline, before each study dose infusion and on Week 28.
In addition to the above exploratory endpoints specified in the protocol, it has been decided to perform a retrospective collection of pre-study pulmonary function tests data and, depending on the completeness and usability of the obtained data, to provide descriptive analyses of pre-study evolution of PFT, and, if feasible, to conduct exploratory analyses on the relationship between this pre-study PFT data, and any change during the study and treatment effect.

4.2 Safety endpoints

Safety will be evaluated from reported adverse events (AEs), respiratory decline events, infusion related reactions, scheduled physical examinations, vital signs, and clinical laboratory test results and concomitant medications.

4.2.1 Adverse events

Adverse events (AE) will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) at the start of the coding activities and will be classified by MedDRA Preferred Term (PT) and System Organ Class (SOC). A Treatment Emergent Adverse Events (TEAE) will be defined as any adverse event that occurs from the time of first study treatment dose administered to the patient until last study visit *i.e.*:

- An AE that was not present prior to receiving the first dose of IMP, or
- An AE that was present prior to receiving the first dose of IMP and increased in intensity after the first IMP administration, or
- An AE that was present prior to receiving the first dose of IMP, with no change in the intensity but with a drug relationship that became related after the first IMP administration.

Tolerability/safety will be assessed over the 28 weeks study period based on:

- The incidence of TEAEs
- The incidence of Treatment Emergent Serious Adverse Events (TESAEs)
- The incidence of respiratory TEAEs and TESAEs
- The proportion of subjects discontinuing study drug due to TEAEs
- All-cause mortality
- Mortality due to respiratory deterioration

4.2.2 Respiratory Decline Events

During the 28 week study period respiratory decline events are recorded. Such “respiratory decline” events are defined as follows:

- Unscheduled visits to a healthcare professional for respiratory status deterioration.
- Urgent care visit for respiratory status deterioration.

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

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

- Acute onset of symptoms (< 30 days in duration)
- New radiographic abnormalities (bilateral ground glass or consolidation on HRCT with no pneumothorax or pleural effusion)
- The absence of an identified infectious etiology by routine clinical practice
- Exclusion of alternative causes by routine clinical practice including:
    a. Left heart failure
    b. Pulmonary embolism
    c. Identifiable cause of acute lung injury

Safety will be assessed based on the incidence of "respiratory decline" and further characterized according to the definitions of IPF-related acute exacerbation.

4.2.3 Infusion related reactions

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.

Infusion related reactions will be classified by MedDRA Preferred Term (PT) and System Organ Class (SOC). Safety will be assess based on the incidence infusion related reactions.

4.2.4 Laboratory endpoints

During the study the following laboratory variables are recorded:

- **Hematology:** Hemoglobin, Hematocrit, Red Blood Cell, White Blood Cell, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, Platelets.
- **Chemistry**: Sodium, Potassium, Chloride, Glucose, Calcium, AST, ALT, Total Bilirubin, Blood Urea Nitrogen, Bicarbonate, Albumin, Creatinine, Alkaline Phosphatase, Total Protein.
- **Coagulation:** Prothrombin Time, Partial Thromboplastin Time, International Normalized Ratio.

Each laboratory result will be categorized in 5 classes of abnormalities according to (see section 8):

- Below LLN CS
- Below LLN NCS
- Normal
- Above ULN NCS
- Above ULN CS

Biological safety will be assessed based on raw test results and change from baseline in raw and categorized laboratory results.

4.2.5 Physical Exams

A complete physical examination is performed during screening and an abbreviated physical exam thereafter. A complete physical examinations will include a review of the following body systems:General appearance, Head, Eyes, Ears, Nose, and Throat, Respiratory, Cardiovascular, Abdomen, Neurologic, Extremities and Dermatologic. Safety will be assessed based on abnormalities (normal, abnormal NCS, abnormal CS) in these body systems.

4.2.6 Vital signs

Vital signs, including Weight, Height, BMI, Heart rate, Respiratory rate, Oxygen saturation, Systolic blood pressure, Diastolic bold pressure are measured in the sitting position at each visit. Vital signs will be assessed based on both raw values and change from baseline to each visit in vital signs measurements.

4.2.7 Concomitant medication

Concomitant medications will be coded according to the latest available version of the WHO-Drug dictionary and tabulated according to the ATC classification.

5 Statistical and Analytical Methods

5.1 General considerations

The statistical analyses are performed in accordance with the ICH E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated. All available efficacy and safety data (according to definition provided in section 4) will be included in data listings and tabulations. Except for the analysis of the primary endpoint (see section 5.2.5.1 Primary efficacy analyses) and for selected secondary endpoints (see section 5.2.5.2 for details), all other analyses will be based on observed data only i.e., no missing data will be imputed.
The statistical analyses will be performed by an external Contract Research Organization (CRO), Venn Life Sciences, under the responsibility of the Sponsor.

5.1.1 Presentation of results

The following statistics will be presented:

- For quantitative variables: number of available data, number of missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum values. When relevant, confidence intervals will be calculated for the mean (Student CI) or the median (Hahn & Meeker 1991).
- For qualitative variables: number of available data, number of missing values number and percentage of observations in each category of the variable. Except if otherwise specified, percentages will be calculated using the number of available data as denominator (*i.e.*, not including missing values). When relevant, confidence intervals of proportions will be calculated using the Clopper-Pearson method (Clopper & Pearson 1934).

5.1.2 Significance testing and estimation

For the primary efficacy analysis (see Section 5.2.5.1), the overall type-one error rate will be set to 0.10 two sided. There will be one single primary efficacy analysis, from which the conclusions on efficacy will be drawn. Consequently, there is no issue of multiplicity of primary analyses and no need to adjust the significance level.
For secondary and exploratory endpoint analyses, 90% CIs will be computed. P-values will also be computed for key secondary efficacy endpoints. No adjustment of the type-one error rate will be

conducted. As a consequence, the results of these tests will have to be interpreted bearing in mind the issue of multiplicity and the increased risk of erroneously obtaining statistically significant results.

For all fitted models (*i.e.*, Linear Models and Linear Mixed Models), the underlying model assumptions (e.g., homoscedasticity, linearity, independence) and the goodness of fit will be check graphically.

Missing values will not be imputed for exploratory analyses. Consequently, for all model involving 'Time' effect, the 'Time' variable will be treated as a continuous variable. However, if the analysis of the residuals of a given model suggests departures from the underlying model assumptions, it will be re-fitted considering 'Time' as a categorial variable (8 modalities) in order to explore non-linear trend in response variable.

5.2 Planned analysis

5.2.1 Demographics and baseline characteristics

The following demographics variables will be summarised by treatment group on the ATS, SAF and the PP analysis data sets (Statistical tables 14.1.1 to 14.1.3):

- Gender
- Age
- Ethnicity / Race
- Number of years since diagnosis of IPF

The following baseline characteristics will be summarised by treatment group on the ATS analysis data set:

- Vital signs (including Weight and Height) at baseline by treatment group (Statistical table 14.1.2)
- Physical exam at baseline by treatment group (Statistical table 14.1.3)
- Haematology at baseline by treatment group (Statistical table 14.1.4)
- Haematology abnormalities at baseline by treatment group (Statistical table 14.1.5)
- Chemistry at baseline by treatment group (Statistical table 14.1.6)
- Chemistry abnormalities at baseline by treatment group (Statistical table 14.1.7)
- Coagulation at baseline by treatment group (Statistical table 14.1.8)
- Coagulation abnormalities at baseline by treatment group (Statistical table 14.1.9)
- Background therapy at baseline (Statistical table 14.1.10)

The following baseline characteristics will be summarised by treatment group on the ATS and the PP analysis data sets:

- King's Brief interstitial Lung Disease and Leicester Cough Questionnaire results at baseline by treatment group (Statistical table 14.1.11.1 to 14.1.11.2)

- High Resolution Computed Tomography measurements at baseline by treatment group (Statistical table 14.1.12.1 to 14.1.12.2)
- Pulmonary Function Tests at baseline by treatment group (Statistical table 14.1.13.1 to 14.1.13.2)
- Six-minute Walk Test distance at baseline by treatment group (Statistical table 14.1.1 to 14.1.2)
- Pentraxin-2 levels at baseline by treatment group (Statistical table 14.1.15.1 to 14.1.15.2)

The following baseline characteristics will be summarised by treatment group on the SAF, the ATS and the PP analysis set:

- Anti-Pentraxin 2 antibodies (ADA) at baseline by treatment group (Statistical table 14.1.16.1 to 14.1.16.3)
- Baseline Genetic Status by treatment group (Statistical table 14.1.17.1 to 14.1.17.3)
- Biomarker levels at baseline by treatment group (Statistical table 14.1.18.1 to 14.1.18.3)

All demographics variables and genetic characteristics of each patient (when available for analysis) will be reported in listing 16.2.4.1 and 16.2.4.2 respectively.

5.2.2 Patient disposition and study discontinuations

Patient disposition will be described using a table (Statistical table 14.1.19) and a flow chart (Figure 14.1). The following variables will be tabulated :

- Number of randomised patients, total and per treatment group
- Number of randomised patient by visit, total and per treatment group
- Number of randomised patients who completed the study treatment as planned (until the 7th cycle on week 24), total and by treatment group
- Number of randomised patients who prematurely discontinued the study treatment (before the 7th cycle on week 24), total and by treatment group
- Number of randomised patients who prematurely discontinued the study treatment before completing the first three cycles and/or who do not have at least one post-cycle 3 evaluation of the primary efficacy criterion (FVC [% predicted])
- Number of randomised patients withdrawn from the study (before week 28) total and by treatment group

The numbers of patient within each dataset (ATS, PP and SAF), globally and by treatment group, will be provided (Statistical table 14.1.20, Listing 16.2.3.1) along with reasons for exclusion from the ATS and PP populations (Statistical table 14.1.21 and 14.1.22 respectively). Reasons for

exclusions from the ATS and PP populations will also be provided in Listing 16.2.3.2, according to ICHE3.

A breakdown of the reasons for study discontinuations (Statistical Table 14.1.23) and for premature study treatment discontinuations (Statistical Table 14.1.24) that can be reasonably considered as unrelated *vs*. related to treatment will be tabulated by treatment group and by major reason for the ATS (classified during the blind review meeting) . All reasons for study discontinuations will be provided in Listing 16.2.1.

All protocol deviations classified during the blinded review meeting according to definitions provided in section 3.1.1 (Major deviations) and 3.1.2 (Minor deviations) will be tabulated by treatment group for the ATS (Statistical table 14.1.25 and 14.1.26 respectively). All major and minor protocol deviations will also be provided in Listing 16.2.2, according to ICHE3.

5.2.3 Medical history – Previous and concomitant medication

All medication will be coded according to the latest available version of the WHO-Drug dictionary at the start of the coding activities. For the study of medical histories/therapy for IPF we will distinguish the one ended before baseline from the ones still present at baseline. More specifically, the following variables will be summarised for the ATS and the SAF analysis data sets:

- Past medical history by treatment group (Statistical table 14.1.27.1 to 14.1.27.2)
- Current medical history by treatment group (Statistical table 14.1.28.1 to 14.1.28.2)
- Previous therapy for IPF by treatment group (Statistical table 14.1.29.1 to 14.1.29.2)
- Current therapy for IPF by treatment group, with information on dose of pirfenidone/nintedanib (Statistical table 14.1.30.1 to 14.1.30.2)
- Previous other therapy by treatment group (Statistical table 14.1.31.1 to 14.1.31.2)
- Current other therapy (Statistical table 14.1.32.1 to 14.1.32.2)

Medical history as well as previous and concomitant therapy for each patient will be reported in Listings 16.2.4.4 and 16.2.4.5 respectively.

5.2.4 Extent of exposure and compliance

Compliance with study treatment will be computed for each subject of the ATS and the PP populations as the proportion of the prescribed IMP that has been actually administered (see section 8). Treatment compliance will then be analyzed globally and by treatment group, as a numerical variable as well as a categorical variable (see section 8, Statistical table 14.1.33.1 to 14.1.33.2).

To analyse the extent of exposure the following variables will be summarised by treatment group for the SAF population (Statistical table 14.3.1):

- number of infusions received
- cumulative volume of IP actually infused
- duration (number of days) between first IP administration and last IP administration

The extent of exposure will also be assessed based on Pentraxin-2 levels. Descriptive statistics for raw values at each visit and for changes from baseline to each visit in Pentraxin-2 levels will be computed by treatment group. This analysis will be performed on both the ATS and the PP dataset (Statistical table 14.3.2.1 to 14.3.2.3, Figures 14.3.1.1 to 14.3.1.2). Individual measurements of Pentraxin-2 levels will be reported in Listing 16.2.6.8.

5.2.5 Efficacy Analysis

5.2.5.1 Primary endpoint analysis

Primary efficacy analysis

Descriptive statistics for (i) raw values at each time point and (ii) change from baseline to each time point in FVC [% predicted] will be computed by treatment group for the ATS analysis dataset (Statistical tables 14.2.1.1.1 and 14.2.1.2.1). The time variation in FVC [% predicted] will be modelled using a linear mixed effect model with random intercept, with raw values at each time point until Week 28 (included) in FVC [% predicted] as dependent variable (outcome), and stratum, treatment, time (continuous variable calculated as the actual number of days since baseline) and treatment by time interaction as explanatory variables (Statistical table 14.2.1.3.1).

The following statistical hypotheses will be tested:

- H0: Absence of difference between the treatment groups.
- H1: A difference exists between the treatment groups.

Least square means for FVC [% predicted] at each time-point (Statistical table 14.2.1.4.1, Figure 14.2.1.1), estimate of slopes, together with their 2-sided 90 and 95% confidence intervals will be presented for both treatment groups.
The comparison of PRM-151 with placebo (Statistical table 14.2.1.5.1) will be carried out by

1. computing the estimate (estimate statement from SAS Proc MIXED) of the between group difference in change from baseline at week 28,
2. computing the corresponding 90% confidence interval
3. computing the p-value of the difference estimate compared to 0.

Statistical significance will be determined using a 2-sided type-one error rate of 0.10.
The listing of the estimates of the random parameters will be provided.

Due to the number of sites planned to recruit and randomize patients in the study, it is expected that each site will include too few patients to allow the inclusion of study site as a covariate in the analysis.

Sensitivity efficacy analysis on the Full Analysis Set population

To assess the effect of including or excluding patient without any post-baseline efficacy measurement from the primary efficacy analysis population (ATS), the primary efficacy analysis described above will be repeated on the Full analysis set population (initially planned in the protocol as the primary efficacy population) and defined as all randomized patients having received at least one administration of the study medication with a baseline and at least one post-baseline assessment of FVC [% predicted] (primary efficacy criterion) available (Statistical tables 14.2.1.1.2, 14.2.1.2.2, 14.2.1.3.2, 14.2.1.4.2 and 14.2.1.5.2).

Sensitivity efficacy analysis on the ATS dataset

The primary efficacy analysis as described above will be repeated with addition of descriptive statistics by stratum, and of the treatment by stratum by time interaction,together with the three two by two interactions, terms in the analysis model (Statistical tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.4 and 14.2.2.5).

In case of a significant qualitative treatment by stratum by time interaction, the data will be carefully examined searching for a potential explanation and the conclusions of the primary efficacy analysis will have to be interpreted cautiously.

The primary efficacy analysis as described above will be repeated without adjusting on stratum in the analysis model (Statistical tables 14.2.1.6.1 to 14.2.1.6.4).

Potential differences in treatment effect according to study site will be addressed by tabulating both raw values of FVC [% predicted] and change from baseline to each visit in FVC [% predicted] by site on the ATS (Statistical tables 14.2.3.1 and 14.2.3.2), but it is expected that due to the small number of patients within each site no precise estimates will be obtained for most of the sites.

Sensitivity efficacy analysis on the PP dataset

The primary efficacy analysis as described above will be repeated on the PP analysis data set (Statistical tables 14.2.1.1.3, 14.2.1.2.3, 14.2.1.3.3, 14.2.1.4.3 and 14.2.1.5.3).

Initially planned primary efficacy analysis (ATS and FAS)
The initially planned primary efficacy analysis will be computed on both the FAS and the ATS: Descriptive statistics for (i) raw values at baseline and week 28 and (ii) for change from baseline to Week 28 in FVC [% predicted] will be computed by treatment group. The mean change from baseline to Week 28 in FVC [% predicted] will be compared between treatment groups using an ANOVA model with treatment group and stratum as explanatory variables. This analysis will use Multiple Imputation relying on monotone regression methods (both efficacy variables including 6MWD, DLCO and other variables such as gender or age can be used in the imputation model) for missing data at week 28. Least square means for changes from baseline to Week 28 in FVC [% predicted], together with their 2-sided 90 and 95% confidence intervals will be presented for each treatment

groups (Statistical table 14.2.4.1 and 14.2.4.2). The mean difference between the two groups will also be presented with its 2-sided 90 and 95% confidence intervals.

5.2.5.2 Secondary efficacy analyses

For all secondary efficacy endpoints, the analyses will be based on observed data only *i.e.*, no data will be imputed. All the following analyses will be performed on both the ATS and the PP analysis data set.

SO1: *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma (normal + mild LAA) and interstitial lung abnormalities (ILA) as quantified on high-resolution CT (HRCT) imaging analysis, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF.*

HRCT is performed at baseline and W28. Descriptive statistics will be computed by treatment group for baseline, week 28 and change from baseline to Week 28 in total lung volume and volume (in ml and % of total lung volume) of parenchyma features representative of normal lung (normal + mild LAA) and representative of interstitial lung abnormalities (ILA) as quantified by HRCT imaging (Statistical table 14.2.5.1.1 and 14.2.5.1.2). A model similar to that of the primary analysis (see section 5.2.5.1) will be used to compare the two groups (Statistical tables 14.2.5.2.1 to 14.2.5.4.2). Individual's measurement of total lung volume and volume of parenchymal features quantified by HRCT imaging will be reported in Listing 16.2.6.3.

SO2: *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

The same model as the one for the primary analysis (see section 5.2.5.1) will be used for each subgroup (Statistical table 14.2.6.1.1 to 14.2.6.3.2). All measurements of FVC [% predicted] will be reported in Listing 16.2.6.1.

SO3: *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung (defined as normal + mild LAA) parenchyma and interstitial lung abnormalities* (ILA) *as quantified on HRCT imaging analysis, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

Descriptive statistics will be computed by treatment group and stratification level for week 0, week 28 and change from baseline to Week 28 in total lung volume and volume (in ml and % of total lung volume) of parenchyma features representative of normal (normal + mild LAA) lung and representative of interstitial lung abnormalities (ILA) as quantified by HRCT imaging. A model similar to that of the primary analysis (see section 5.2.5.1) will be used to compare the two groups

(Statistical table 14.2.7.1.1 to 14.2.7.4.2). Individual's measurement of total lung volume and volumes of parenchymal features quantified by HRCT imaging will be reported in Listing 16.2.6.3.

SO4: *To assess the tolerability and safety of PRM-151 in subjects with IPF through Week 28.*

See Section 5.2.6 safety analysis.

SO5: *To assess the ability of PRM-151 to reduce disease-related events associated with mortality*

See Section 5.2.6 safety analysis.

SO6: *To determine the effect size of PRM-151 relative to placebo on pulmonary function in addition to mean change in FVC% predicted*

To determine the effect size of PRM-151 relative to placebo on pulmonary function, descriptive qualitative statistics and Odds-Ratios (PRM-151 /Placebo) with their 90% CIs will be calculated by treatment group and stratification level for:

- Subjects with a decline in FVC [% predicted] of ≥ 5% and ≥ 10% from baseline to week 28.
- Subjects with a decline in FVC [ml] of ≥ 100ml and ≥ 200ml from baseline to week 28.
- Subjects with an increase in FVC [% predicted] of ≥ 5% and ≥10% from baseline to week 28.
- Subjects with an increase in FVC [ml] of ≥ 100 ml and ≥ 200 ml from baseline to week 28.
- Subjects with stable disease by FVC [% predicted], defined as a change in FVC [% predicted] of < 5% from baseline to week 28.
- Subjects with stable disease by FVC in ml, defined as a change in FVC [ml] of < 100ml from Baseline to week 28.

For each of these endpoints treatment groups will be compared using the Cochran-Mantel-Aenszel general association test available in the SAS Freq procedure, adjusting for the Stratum effect (Statistical table 14.2.8.1 to 14.2.8.2). Due to the small sample-size, the exact version of the test will be used. Odds ratio (with 90% CI) together with p-values will be reported.

SO7: *To determine the effect size of PRM-151 relative to placebo on 6-minute walking distance*

The same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used (Statistical tables 14.2.9.1.1 to 14.2.9.5.2). All results of the 6-minute walk test will be reported in Listing 16.2.6.2.

SO8: *To determine the effect size of PRM-151 relative to placebo on DLCO.*

The same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used (Statistical tables 14.2.10.1.1 to 14.2.10.5.2). All DLCO measurements will be reported in Listing 16.2.6.1.

SO9: *To determine the correlation between change in FVC [% predicted] and total lung volume and volume of ILA on HRCT from Baseline to Week 28*

Correlation between change from baseline in FVC[% predicted] and (i) total lung volume (Statistical table 14.2.11.1.1 and 14.2.11.1.2, Figures 14.2.2.1.1 and 14.2.2.1.2) and (ii) volume of ILA on HRCT will be produced along with the corresponding scatter plots (Statistical table 14.2.11.2.1 and 14.2.11.2.2, Figures 14.2.2.2.1 and 14.2.2.2.2).

5.2.5.3 Exploratory efficacy analyses

For all exploratory efficacy endpoints, the analyses will be based on observed data only *i.e.*, no data will be imputed.

EO1: *To evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC % predicted, FVC in ml and 6 minute walking distance, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF and separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

A model similar to that of the primary analysis (see section 5.2.5.1) but with the addition of random slopes will be used to evaluate on both the ATS and the PP data sets the efficacy and estimate the size of effect of PRM-151 relative to placebo in time variations in FVC [% predicted] (Statistical tables 14.2.12.1.1 to 14.2.13.3.2, Figures 14.2.3.1 to 14.2.3.2), FVC [ml] (Statistical tables 14.2.14.1.1 to 14.2.15.5.2, Figures 14.2.4.1 to 14.2.5.2) and 6MWD (Statistical tables 14.2.16.1.1 to 14.17.5.2, Figures 14.2.6.1 to 14.2.7.2). The individual slopes and intercepts will be listed (Listings 16.2.6.9 to 16.2.6.11) and summarized. Statistical inference (90% CI and p-values) on the slope difference between treated and placebo groups will be reported.

EO2: *To assess the impact of PRM-151 on disease related symptoms and quantitative imaging.*

Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume), representative of interstitial lung abnormalities (ILA) will be computed, comparing PRM151 *vs.* placebo (separately) in patients with SVC breathhold at CT scanning ≥90% of SVC supine, with a similar approach to the one used for the primary analysis (statistical tables 14.2.18.1.1 to 14.2.19.4.2).

For all categories of lung features, the change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) wil be computed in subjects treated with PRM-151 and placebo, depending on the completeness and usability of the obtained data.

Change in Patient Reported Outcomes will be assessed based on the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and Leicester Cough Questionnaire (LCQ). Descriptive statistics for raw values and change from Baseline to each visit in total score of both questionnaire will be computed by treatment group (Statistical tables 14.2.20.1.1 to 14.2.20.2.2 and 14.2.21.1.1 to 14.2.21.2.2, Figures 14.2.8.1 to 14.2.9.2). Differences between treatment groups in change from baseline to week 28 for total score of each questionnaire will be tested using a similar approach to the one used for the primary ananlysis (see section 5.2.5.1). These analysis will be performed on both the ATS and the PP data sets (Statistical table 14.2.20.3.1 to 14.2.20.5.2 and 14.2.21.3.1 to 14.2.21.5.2). All results of K-BILD and LCQ will be reported in Listings 16.2.6.4 and 16.2.6.5.

For the LCQ, in addition to the above approach, frequency of patients with changes below or above 1.3 (identified as the minimal important difference) will be tabulated by treatment groups at week 4, 8, 12, 16, 20, 24 and 28 (Statistical table 14.2.21.6.1 and 14.2.21.6.2).

Descriptive statistics for raw values at each visit and change from baseline to each visit in anti-Pentraxin-2 antibodies measurements will be computed by treatment group. This analysis will be performed on both the ATS and the PP dataset (Statistical 14.2.22.1.1 to 14.2.22.2.2). Individual measurements of anti-pentraxin-2 antibodies will be reported in Listing 16.2.6.8.

EO3: *To assess the use of quantitative imaging in IPF*

The correlation between baseline FVC [% predicted], DLCO (corrected for Hb, [% predicted]), TLC by nitrogen washout, PROs and 6MWD and total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of ILA by quantitative imaging, as well as change from Baseline to Week 28 in FVC [% predicted], DLCO (corrected for Hb, [% predicted]), TLC by nitrogen washout, PROs and 6MWD and change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of ILA will be computed. This analysis will be performed on both the ATS and the PP dataset (Statistical tables 14.2.23.1.1 yo 14.2.23.1.2).

For all categories of lung features the correlation between (i) change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) and (ii) change from baseline to week 28 in FVC [% predicted] will be computed. This analysis will be performed on both the ATS and the PP dataset (Statistical tables 14.2.23.2.1 yo 14.2.23.2.2).

For all categories of lung features the correlation between (i) change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) and (ii) change

from baseline to week 28 in DLCO will be computed. This analysis will be performed on both the ATS and the PP datasets (Statistical table 14.2.23.3.1 yo 14.2.23.3.2).

The impact of inspiratory effort on results of HRCT quantitative imaging will be assessed by (Statistical table 14.2.23.4.1 to 14.2.23.4.2, Figure 14.2.10.1 to 14.2.10.2):
1. Calculating the proportion of patients performing spirometry guided HRCT with a SVC breathhold at CT scanning ≥90% of SVC supine at baseline and at week 28
2.The correlation of SVC breathhold at CT scanning and SVC supine at baseline and at week 28
3.The correlation between (i) baseline Total lung volume by quantitative imaging and (ii) baseline TLC by nitrogen washout, seperately for patients with SVC breathhold at CT scanning ≥90% of SVC supine, and for patients with SVC <90% or not receiving spirometry-guided HRCT.

EO4: *To assess the impact of PRM-151, disease pathogenesis and disease progression on exploratory serum, cellular and genetic biomarkers*

To assess the impact of PRM-151 on exploratory biomarkers, descriptive statistics for change from baseline to week 28 in biomarkers will be computed by treatment group and by baseline genetic status (MUC5B and TLR polymorphism separately). These analysis will be performed on both the ATS and the PP dataset (Statistical table 14.2.24.1 and 14.2.24.2). Individual biomarker values will be reported in Listing 16.2.6.6. All or part of these analyses may be provided at a later stage than the rest of the analyses described in the SAP, might the corresponding data not be available at the time of the database lock. It is currently anticipated that baseline genetic status will be avialable, but biomarkers will not.

Additional exploratory analysis
The relationship between Anti-Pentraxin 2 antibodies (ADA) presence and level of FVC [% predicted] in time will be studied by modelling the influence of presence/absence (and/or level) of ADA in the repeated measures mixed model used for the primary efficacy analysis (see section 5.2.5.1) and if relevant using non-parametric spline functions. The most parcimonious model will be chosen on the basis of the AIC (Statistical table 14.2.25.1 and 14.2.25.2).

Exploratory analysis of PK/PD relationship

Descriptive statistics and correlation will be computed to explore the relationship of Pentraxin-2 levels vs FVC [% predicted]/FVC [ml]/slope of FVC ml at week 24 and 28, and the relationship of Pentraxin-2 vs other PFTs/PROs/6MWT. If relevant the corresponding scatter plot will be produced.

Exploratory analysis of relationship between Pentraxin-2 levels and ADA
Correlation coefficient between Pentraxin-2 levels and ADA titer at week 28 will be computed (Statistical tables 14.2.27.1 and 14.2.27.2) and a scatterplot prepared (using logarithmic coordinates for titers).

Exploratory analysis of acute exacerbations
Tabulation of each type of acute exacerbations will be produced (Statistical table 14.2.28.1.1 and 14.2.28.1.2). Descriptive statistic and Kaplan-meier curve will be computed by treatment group for time to first reported acute exacerbation (Statistical tables 14.2.28.2.1 and 14.2.28.2.2).

5.2.6 Safety analyses

Safety analysis will be based on the incidence, intensity, and type of adverse events, incidence of respiratory decline, Infusion related reactions, and clinically significant changes in the subject's physical examination, vital signs and clinical laboratory results. Safety variables will be tabulated and presented for all subjects who have received any amount of study medication.

5.2.6.1 Adverse events

Adverse event listings:

AE listings will be presented and sorted by subject, start date (calendar date and day from first IMP intake), primary system organ class, preferred term and verbatim text for all adverse events recorded during the study and will include time since last IMP dose and duration of each episode.

The following listings will be produced:

- Listing of Adverse Events (Listing 16.2.7.1): All adverse events for each patient, including the same event on several occasions, giving both preferred term and the original term used by the investigator. The listing will be sorted by site and by treatment group and should include: Patient identifier / Age, race-ethnicity, sex, weight, height / The adverse event (preferred term, reported term) / Duration of the adverse event / Severity (mild, moderate, severe) / Seriousness (serious, non-serious) / Action taken with study drug (dose reduced, treatment interrupted-delayed, treatment permanently discontinued-omitted, none, not applicable) / Outcome (resolved, resolved with sequelae, ongoing, unknown) / Relationship to study drug (not related, possibly related, probably related) / Date of onset or date of clinic visit at which the event was discovered / Timing of onset of the adverse event in relation to last dose of test investigational product (when applicable) / Study treatment at time of event or most recent study treatment taken / investigational product dose in absolute amount, mg/kg at time of event / Duration of test investigational product treatment.

- Listing of Deaths (Listing 16.2.7.2) and Serious Adverse Events containing the same information as above.

Adverse events tabulations:

Tabulation of adverse events will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events (if

relevant). The following tables will be produced for the whole SAF population as well as by treatment group:

Summary of AE (Statistical Table 14.3.3):

- Any AE
- Any TEAE
- Any TEAE leading to permanent study treatment discontinuation
- Any TEAE leading to study discontinuation
- Any TEAE of severe intensity
- Any possibly or probably related TEAE
- Any SAE
- Any TESAE
- Any TESAE leading to study treatment permanent discontinuation
- Any TESAE leading to study discontinuation (optional)
- Any TESAE considered related to the study treatment
- Deaths (if any)
-

Detailed Tables on TEAEs:

- All TEAE by SOC and PT (Statistical Table 14.3.4.1)
- Most frequent TEAEs by SOC and PT and decreasing frequency (Statistical Table 14.3.4.2)
- All possibly or probably related TEAEs by SOC and PT (Statistical Table 14.3.4.3)
- All TEAE by SOC, PT and intensity (Statistical Table 14.3.4.4)
- All TEAE leading to permanent study drug discontinuation by SOC and PT (Statistical Table 14.3.4.5, only produced if more than 5 events)
- All TEAE leading to permanent study discontinuation by SOC and PT (Statistical Table 14.3.4.6, only produced if more than 5 events)

Detailed Tables on TESAEs:

- Any TESAE by SOC and PT (Statistical Table 14.3.5.1)
- All possibly or probably related TESAEs by SOC and PT (Statistical Table 14.3.5.2, only produced if more than 5 events)
- All TESAE by SOC, PT and intensity (Statistical Table 14.3.5.3)
- All TESAE leading to permanent study drug discontinuation by SOC and PT (Statistical Table 14.3.5.4, only produced if more than 5 events)
- All TESAE leading to permanent study discontinuation by SOC and PT (Statistical Table 14.3.5.5, only produced if more than 5 events)
- Death: all causes of mortality and mortality due to respiratory declines (Statistical Table 14.3.5.6)

5.2.6.2 Respiratory decline events

Tabulation of respiratory decline events will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events. The following tables will be produced for the whole SAF population as well as by treatment group:

- All respiratory decline events by PT (Statistical tables 14.3.6.1)
- All respiratory decline events by PT and intensity (Statistical tables 14.3.6.2)
- All respiratory decline events by PT and seriousness (Statistical tables 14.3.6.3)

5.2.6.3 Infusion related reactions

Tabulation of infusion related reactions will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events. The following tables will be produced for the whole SAF population as well as by treatment group:

- All infusion related reactions by PT (Statistical tables 14.3.7.1.1)
- All infusion related reactions by PT and intensity (Statistical tables 14.3.7.1.2)
- All infusion related reactions by PT and seriousness (Statistical tables 14.3.7.1.3)

The potential influence of Anti-Pentraxin 2 antibodies (ADA) and occurrence of IRR will be studied by producing the same tables as described above breaking down the patients according to presence/absence of ADA (Statistical tables 14.3.7.2.1, 14.3.7.2.2 and 14.3.7.2.3).

5.2.6.4 Laboratory safety variables

Table of laboratory safety variables:

Laboratory evaluations will be summarized by visit and by treatment group on the SAF population. For each hematology, chemistry and coagulation variables we will compute:

- Quantitative descriptive statistics on both raw values and change from baseline (Statistical tables 14.3.8.1, 14.3.9.1 and 14.3.10.1)
- Qualitative descriptive statistics (individual patient changes):
    - Number of patients with values: below LLN CS, below LLN NCS, normal, above ULN NCS, above ULN CS (Statistical table 14.3.8.2, 14.3.9.2 and 14.3.10.3)
    - Shift Tables from baseline to each visit (Statistical table 14.3.8.3, 14.3.9.3 and 14.3.10.3)

Depending of their number the clinically significant laboratory abnormalities will not be tabulated but rather presented in individual data listings (Listings 16.2.8.1 to 16.2.8.4).

Figures on laboratory safety variables:

"Shift" figures compare the initial value and the on-treatment values of a given laboratory measurement for each patient by locating the point defined by the baseline value on the abscissa and the worst subsequent value on the ordinate will be produced. The line of equality (on-treatment value=baseline) will be added. When available, the LLN and ULN will be displayed on the graph. Shift figures will be produced for all hematologic, chemistry and coagulation variables (Figures 14.3.2.1 to 14.3.2.3).

To facilitate the exploration of potential Drug-Induced Liver Injury (DILI), eDISH (Evaluation of Drug-Induced Serious Hepatotoxicity) plots, plotting peak total bilirubin level versus peak ALT level, both expressed as multiples of the upper limit of normal on a base 10 logarithmic scale, together with mlines identifying the normal range and 2 times the upper lipit of the normal range for total bilirubin and three times the upper limit of the normal range for ALT, will be presented.

Listing of laboratory safety variables:

Listings of all safety-related laboratory test including pregnancy test (Listings 16.2.8.1 to 16.2.8.4) will be prepared, presenting patient id, identification of time point, age, sex, race-ethnicity, weight and IMP dose, identification of laboratory test, raw result, evaluation (normal, abnormal…), investigator judgment on clinical significance on abnormal values. This listing will be presented by study site and by treatment group.

A listing of each abnormal individual value will be prepared, using the same display as listing 16.2.8.

5.2.6.5 Physical exams

For all the variables collected during physical examinations at baseline, the frequencies of normal, abnormal NCS and abnormal CS values will be reported by treatment group (Statistical table 14.3.11). All individual measurements collected at baseline and during the subsequent visits will be provided in Listing 16.2.9.1.

5.2.6.6 Vital signs

- Quantitative descriptive statistics: mean, median, standard deviation, min, max based on raw values and change from baseline (Statistical tables 14.3.12.1 and 14.3.12.2)
- Qualitative descriptive statistics (individual patient changes):
    - Proportion of patients with abnormal values (Statistical table 14.3.12.3)

- Shift Tables presenting the number of patients with normal/abnormal values at baseline and then at each cycle (Statistical table 14.3.12.4)

All individual measurements will be provided in Listing 16.2.9.2.

5.2.6.7 Concomitant medication

A listing of all concomitant medications will be provided (Listing 16.2.9.3).
Two tables with the proportions of subjects in the SAF population taking each concomitant medication will be provided for:

- Concomitant medications at baseline (started before baseline and stopped after baseline or still ongoing at end of treatment) by treatment group (Statistical table 14.3.13.1).
- Concomitant medications started after baseline by treatment group (Statistical table 14.3.13.2).

A table summarizing pirfenidone and nintedanib use (proportion of patients using each drug) and dose (descriptive staitstics for continuous variables) by treatment group will be prepared on the SAF population (Statistical table 14.3.13.3).

5.3 Statistical/Analytical issues

5.3.1 Adjustments for Covariates

All comparisons of change from baseline to a given visit between treatment groups performed using ANOVA models and pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF, are adjusted for stratification levels.

Analysis of time variation in a given variable using Linear Mixed Models and pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF, are all adjusted for baseline measurements of the response variable and stratification levels.

5.3.2 Handling of Dropouts or Missing Data

Missing data in efficacy analysis:

The statistical model (linear mixed models for repeated measures) used for the primary and most secondary efficacy analyses will be used without imputation of missing values and are valid under the assumption of missingness at random.
Multiple imputation techniques will be used for the sensitivity analysis on the initially planned primary analysis (see Section 5.2.5.1).

All available efficacy and safety data will be included in data listings and tabulations.

Missing or incomplete dates:

For all listings, missing or incomplete dates will be left as they were recorded.

For calculation / sorting / assignation based on dates (*e.g.*, treatment emergent AEs, concomitant medications…), the following rules will apply:

- The most conservative approach will be considered (*i.e.*, if the onset date of an AE/concomitant medication is missing / incomplete, it will be assumed to have occurred during the study treatment phase (*i.e.*, a TEAE for AEs) except when the partial onset date or other available data indicates differently (*e.g.*, start date day missing, but month before the month of baseline date, or stop date before baseline date).
- Medical history or disease diagnosis with missing/incomplete date will be assumed to have occurred before any study treatment except when the partial onset date or other available data indicates differently.
- Assignations based on dates will be reviewed and confirmed or infirmed during the data review meeting
- Missing or partial start or end dates of IMP administration, if any, will be reviewed during the data review meeting.

5.3.3 Interim Analyses and Data Monitoring

No formal interim data analysis is planned for the study.

A blinded DMC will be established to review safety data from this study, thereby better ensuring the safety of study participants. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will be constituted of independent clinicians expert in the field of IPF and clinical research. A formal charter will be established for the conduct of the DMC.

The committee is planned to review the safety data in an unblinded manner, and the efficacy data will be provided semi-blinded by group. However, DMC may request study drug treatment code for group in order to complete their assessment of safety/benefit risk. This request will only be made to the unblinded statistician, as stated in the DMC Charter.

5.3.4 Multicentre studies

This study is planned to be conducted in 18 study sites in 8 countries. Because of the too small expected numbers of patients within sites, all the analysis will be performed on the pooled data over countries and study sites.

5.3.5 Multiple Comparison/Multiplicity

There will be one single primary efficacy analysis, from which the conclusions on efficacy will be drawn. Consequently, there is no issue of multiplicity of primary analyses and no need to adjust the significance level.

5.3.1 Use of an "Efficacy Subset" of Patients

Two efficacy analyses populations are defined, the ATS and the PP. The definition of these populations is available in Section 3. The primary efficacy analysis will be conducted on the ATS. No patient with available post-treatment efficacy data are excluded from the ATS and, consequently from the primary efficacy analysis.

The PP population will be used to conduct a sensitivity analysis and assess the robustness of the primary efficacy analysis conclusions. Any substantial difference between the two analyses will be explored and discussed.
In addition, the SAP planned to conduct the primary analysis on the Full analysis Set. This was then changed to the ATS. Nevertheless, the initially planned analysis on the FAS will be conducted and provided as an additional sensitivity analysis to further assess the robustness of the primary efficacy analysis conclusions and in particular to assess the impact of excluding patient without any post-baseline efficacy measurement from the FASATS population. Any substantial difference with the result obtained for the primary efficacy analysis on the ATS will be explored and discussed.

5.3.2 Active-Control Studies Intended to Show Equivalence

Not applicable.

5.3.3 Examination of Subgroups

Sensitivity analysis of the primary endpoint and some secondary efficacy analyses aim at exploring difference in response variables between the levels of stratification. See sections 5.2.5.1 and 5.2.5.2 for details.

5.4 Data handling conventions

5.4.1 Baseline definitions

For both the efficacy and safety endpoints the last observation prior to the first dose of study treatment administration will be used as the baseline value. This will usually correspond to the measurement performed at day1 week 0 before first-dose. However, in case of missing value at day 1 week 0 the last available value recorded during screening will be used as baseline value.

5.4.2 Retest, Outliers

5.4.2.1 Retests

The retests will be managed as follow:

- Any retest before baseline : the last available value recorded before baseline (day1 week 0) will be used as the baseline
- Any other retest: data will be reviewed and decision will be made during the blind review on the basis of the following rules:
    - Retest on efficacy data: non-missing value the closest to the scheduled visit will be used
    - Retest on safety data: the worst recorded value will be used

5.4.2.2 Outliers

All outlier data will be reviewed during the data review meeting and decisions regarding their use in the statistical analyses will be made.

5.4.3 Unscheduled visits

All unscheduled visit data will be presented in the individual data listings and used in all safety analyses. In case of missing study visit in efficacy analyses any unscheduled data visit falling within the corresponding time frame will be used in per-visit tabulations (i.e., descriptive statistics).

5.4.4 Visit windowing

For the tabulation of descriptive statistics and analyses at specific time points, the following rules will be followed: the time window corresponding to a given visit will be the interval between the mid point between this visit and the preceding one and the visit and the following one, as described in the table below.

Visit	Visit window
Screening	Day-28 to Day-1
Week 0	Week0-Day 1
Week 4 (Day 28)	Day 15-Day 42
Week 8 (Day 56)	Day 43-Day 70
Week 12 (Day 84)	Day 71-Day 98
Week 16 (Day 112)	Day 99-Day 126
Week 20 (Day 140)	Day 127-Day 154
Week 24 (Day 168)	Day 155-Day 182
Week 28 (Day 196)	Day 183-Day 210

If several actual visits fall within the same visit window, the actual visit the closest to the theoretical day will be used for that visit.

For most of the repeated-measures analyses presented in section 5.2.5, the models proposed will use real time (days since baseline) instead of theoretical visit days, so windowing is only necessary for descriptive statistics.

Imaging endpoints are scheduled both at Week 0 (Baseline) and Week 28. The baseline CT scan should be performed before start of first infusion on Week 0 Day 1, or within the week before, i.e. between Day-7 and Week 0 Day 1. The Week 28 CT scan should be performed on Week 28 +/- 14 days. Any CT Scan performed outside these windows will be regarded as a protocol deviation (see section 3.1).

6 Modifications from the statistical sections in the protocol

6.1 Change in the primary efficacy analysis

According to the protocol, the primary efficacy analysis was to be the Full Analysis Set (FAS), defined as all randomized patients having received at least one administration of the study medication with a baseline and at least one post-baseline assessment of FVC [% predicted] (primary efficacy criterion) available.
Limiting the population to subjects having at least one post-baseline assessment of FVC [% predicted] draws the efficacy population further from the intention to treat paradigm than the exclusion of only untreated patients. Consequently, it has been decided to change the primary efficacy analysis population to the All Treated Set (ATS, see section 3.2) defined as all randomized subjects who have received at least one administration of the investigational medicinal product (IMP).

In addition to this change of population, it has been decided to change the analysis model from the initially planned ANOVA model on change from baseline to week 28 to a linear mixed effect model

with random intercept using all measurements available until Week 28 used to compute the estimate of the between group difference in change from baseline at week 28.

6.2 Changes in secondary efficacy analyses

All secondary efficacy analyses will be performed on both the ATS and the PP.

To be consistent with the primary efficacy analysis, the same analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma (normal + mild LAA) and interstitial lung abnormalities (ILA) as quantified on high-resolution CT (HRCT) imaging analysis (SO1).

To be consistent with the primary efficacy ananlysis, the same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF (SO2).

To be consistent with the primary efficacy ananlysis, the same analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung (defined as normal + mild LAA) parenchyma and interstitial lung abnormalities (ILA) as quantified on HRCT imaging analysis (SO3).

Odds ratios wil be computed in addition to quantitative statistics to determine (SO6) the effect size of PRM-151 relative to placebo on pulmonary function and mean change in FVC% predicted.

To be consistent with the primary efficacy ananlysis, the same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used to determine the effect size of PRM-151 relative to placebo on 6MWD (SO7) and DLCO (SO8).

6.3 Changes in eploratory efficacy analyses

All exploratory efficacy analysis will be performed on both the ATS and the PP.

It was initially planned (EO1) to evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC % predicted, FVC in ml and 6 minute walking distance using mixed models with random intercepts. To obtain a better decription of individual variability, both random intercepts and random slopes will be used.

The following not initialy planned exploratory analysis were added (see section 5.2.5.3 for details):

- To assess the use of quantitative imaging in IPF (E03)

- To explore the relationship between Anti-Pentraxin 2 antibodies (ADA) presence and level of FVC [% predicted] in time
- To explore PK/PD relationship.
- To explore relationship between Pentraxin-2 levels and ADA
- To explore acute exacerbations

7 Software documentation

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

8 Derived data

Derived variable	Derivation algorithm
Change from baseline to visit V (continuous)	Change from baseline of variable $X=X_{(Visit\ V)}-X_{(Baseline)}$ o Negative values indicate a decrease in X o Positive values indicate an increase in X
Percent change from baseline to visit V (continuous)	Percent change from baseline of variable $X=100*[X_{(Visit\ V)}-X_{(Baseline)}]/\ X_{(Baseline)}$ o Negative values indicate a decrease in X o Positive values indicate an increase in X
Treatment compliance	Continuous variable: The compliance C_i for patient *i* will be computed according to: $$C_i = \frac{D_i^t * 100}{D_i^p}$$ where D_i^p mg is the total amount (mg) of IP prescribed to patient *i* and D_i^t is the total amount (mg) of IP actually taken by the patient during the study i.e., before the end of study for patient *i*.
Treatment compliance (categorical)	Categorial variable with three modalities: • $C_i < 80\%$ • $80\% \leq C_i < 120\%$ • $C_i \geq 120\%$
Event Duration	(End Date) – (Start Date) + 1

9 Tables, Figures and Listings

9.1 List of tables

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14.1.1 to 14.1.3	Demographics (11.2)
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14.1.3	Physical examination at baseline
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14.1.6	Chemistry at baseline
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14.1.8	Coagulation at baseline
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14.1.10	Background therapy at baseline
14.1.11.1 to 14.1.11.2	K-BILD and Leiceister Cough Questionnaires at baseline
14.1.12.1 to 14.1.12.2	High Resolution Computed Tomography at Baseline
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14.1.19	Disposition of patients (10.1)
14.1.20	Datasets analyzed (11.1)
14.1.21	Reasons for exclusion from the FAS
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14.1.29.1 to 14.1.29.2	Previous therapy for IPF
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14.1.33.1 to 14.1.33.2	Treatment compliance (11.3)
n°	**Efficacy Results**
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14.2.1.2.1 to 14.2.1.2.3	**(PO1) Primary Efficacy / Sensitivity Analysis: FVC [% predicted] - change from baseline to each visit**
14.2.1.3.1 to 14.2.1.3.3	**(PO1) Primary Efficacy / Sensitivityy Analysis: Least Square Means for FVC [% predicted] at each visit**
14.2.1.4.1 to 14.2.1.4.3	**(PO1) Primary Efficacy / Sensitivity Analysis: Anova table**
14.2.1.5.1 to 14.2.1.5.3	**(PO1) Primary Efficacy / Sensitivity Analysis: Model parameter estimates**
14.2.1.6.1 to 14.2.1.6.4	**(PO1) Primary Efficacy / Sensitivity Analysis without adlusting for stratum**
14.2.2.1	**(PO1) Sensitivity Analysis: FVC [% predicted] - raw values at each visit by stratum**
14.2.2.2	**(PO1) Sensitivity Analysis: FVC [% predicted] - change from baseline to each visit by stratum**
14.2.2.3	**(PO1) Sensitivity Analysis: FVC [% predicted] - Least Square Means at each visit by stratum**
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14.2.3.1	**(PO1) Sensitivity analysis: FVC [% predicted] - raw values at each visit by site**
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14.2.4.1 to 14.2.4.2	**(PO1) Sensitivity Analysis: Initially planned primary efficacy ananlysis**
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14.2.6.1.1 to 14.2.6.1.2	(SO2) Secondary Efficacy Analysis: FVC [% predicted] - Least Square Means at each visit separately for each stratum
14.2.6.2.1 to 14.2.6.2.2	(SO2) Secondary Efficacy Analysis: FVC [% predicted]s - Anova table separately for each stratum
14.2.6.3.1 to 14.2.6.3.2	(SO2) Secondary Efficacy Analysis: FVC [% predicted] - Model parameter estimates separately for each stratum
14.2.7.1.1 to 14.2.7.1.2	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Descriptive statistics seaprately for each stratum

14.2.7.2.1 to 14.2.7.2.2	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Least Square Means separately for each stratum
14.2.7.3.1 to 14.2.7.3.2	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Anova table separately for each stratum
14.2.7.4.1 to 14.2.7.4.2	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Model parameter estimates separately for each stratum
14.2.8.1 to 14.2.8.2	(SO6) Secondary analyses: Categorial analysis of FVC [% predicted]
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14.2.9.3.1 to 14.2.9.3.2	(SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - Least Square Means
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14.42.5.1 to 14.42.5.2	(SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - Model parameter estimates
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14.2.11.2.1 to 14.2.11.2.2	(SO9) Secondary Efficacy Analysis: Correlation between FVC [% predicted] and volume of ILA on HRCT
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14.2.12.2.1 to 14.2.12.2.2	(EO1) Exploratory analyses: FV [%predicted] - Least Square Means
14.2.12.3.1 to 14.2.12.3.2	(EO1) Exploratory analyses: FV [%predicted] - Model parameter estimates
14.2.13.1.1 to 14.2.13.1.2	(EO1) Exploratory analyses: FV [%predicted] - Anova table separately for each stratum
14.2.13.2.1 to 14.2.13.2.2	(EO1) Exploratory analyses: FV [%predicted] - Least Square Means separately for each stratum
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14.2.14.1.1 to 14.2.14.1.2	(EO1) Exploratory analyses: FV [ml] - raw values at each visit

14.2.14.2.1 to 14.2.14.2.2	(EO1) Exploratory analyses: FV [ml] - change from baseline to each visit
14.2.14.3.1 to 14.2.14.3.2	(EO1) Exploratory analyses: FV [ml] - Least Square Means
14.2.14.4.1 to 14.2.14.4.2	(EO1) Exploratory analyses: FV [ml] -Anova table
14.2.14.5.1 to 14.2.14.5.2	(EO1) Exploratory analyses: FV [ml] - Model parameter estimates
14.2.15.1.1 to 14.2.15.1.2	(EO1) Exploratory analyses: FV [ml] - raw values at each visit separately for each stratum
14.2.15.2.1 to 14.2.15.2.2	(EO1) Exploratory analyses: FV [ml] - change from baseline to each visit separately for each stratum
14.2.15.3.1 to 14.2.15.3.2	(EO1) Exploratory analyses: FV [ml] - Least Square Means separately for each stratum
14.2.15.4.1 to 14.2.15.4.2	(EO1) Exploratory analyses: FV [ml] - Anova table separately for each stratum
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14.2.16.1.1 to 14.2.16.1.2	(EO1) Secondary Efficacy Analysis: 6 Minute Walk Distance- Anova table
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14.2.17.1.1 to 14.2.17.1.2	(EO1) Secondary Efficacy Analysis: 6 Minute Walk Distance - raw values at each visit separately for each stratum
14.2.17.2.1 to 14.2.17.2.2	(EO1) Secondary Efficacy Analysis: 6 Minute Walk Distance - change from baseline to each visit separately for each stratum
14.2.17.3.1 to 14.2.17.3.2	(EO1) Secondary Efficacy Analysis: 6 Minute Walk Distance- Least Square Means separately for each stratum
14.2.17.4.1 to 14.2.17.4.2	(EO1) Secondary Efficacy Analysis: 6 Minute Walk Distance- Anova table separately for each stratum
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14.2.18.1.1 to 14.2.18.1.2	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - Descriptive statistics for total lung volume separately in patients with SVC breathhold at CT scanning ≥90% of SVC supine
14.2.18.2.1 to 14.2.18.2.2	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - Least Square Means separately in patients with SVC breathhold at CT scanning ≥90% of SVC supine
14.2.18.3.1 to 14.2.18.3.2	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - Anova table separately in patients with SVC breathhold at CT scanning ≥90% of SVC supine

14.2.18.4.1 to 14.2.18.4.2	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - Model parameter estimates separately in patients with SVC breathhold at CT scanning ≥90% of SVC supine
14.2.19.1.1 to 14.2.19.1.2	(EO2) Exploratory analyses: HRCT image analysis (ILA) - Descriptive statistics for ILA volume separately in patients with SVC breathhold at CT scanning ≥90% of SVC supine
14.2.19.2.1 to 14.2.19.2.2	(EO2) Exploratory analyses: HRCT image analysis (ILA) - Least Square Means separately in patients with SVC breathhold at CT scanning ≥90% of SVC supine
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References

Clopper, C. J., & Pearson, E. S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*, *26*(4), 404-413.
Collard, H. R., Moore, B. B. et al. (2007). Acute exacerbations of idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*, 176(7), 636-643.

Collard, H. R., Yow, E. et al. (2013). Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respiratory research*, 14(1), 73-73.

Hahn, G. J., & Meeker, W. Q. (2011). Statistical intervals: a guide for practitioners (Vol. 328). John Wiley & Sons.

Statistical Analysis Plan

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

PRM-151-202

Versions History

Version Number	Date	Detail
Version 1	20 Dec 2016	Not applicable: First version
Version 2	08 Jun 2017	-Updated Tables Figures and Listings list -Added Pulmonary Vessel Volume as Exploratory Endpoint -Added exploratory efficacy analyses of FVC for patient subsets on either a stable dose of (i) pirfenidone or (ii) on a stable dose of nintedanib. -Added exploratory analysis of available historic data of FVC and associated derivation rule. -Added data handling guidance for details regarding data collected at end of study visit for patients prematurely discontinued from the study. -Added derivation rule for variables derived from HRCT data.

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Contents

Abbreviations and definitions

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
ADA	Anti-Drug Antibodies
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis Of Variance
AST	Aspartate aminotransferase
ATS	All Treated Set
BMI	Body Mass Index
CRO	Contract Research Organization
CS	Clinically Significant
CT	Computed Tomography
DLCO	Diffusing capacity of the Lung for Carbon monoxide (CO)
DMC	Data Monitoring Committee
EO	Exploratory Objective
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
HRCT	High-Resolution Computed Tomography
ICH	International conference of harmonization
ILA	Interstitial Lung Abnormality
IMP	Investigational Medical Product
IP	Investigational Product
IPF	Idiopathic Pulmonary Fibrosis
IV	Intravenous
K-BILD	King's Brief Interstitial Lung Disease Questionnaire
LCQ	Leicester Cough Questionnaire
LLN	Lower Limit Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Non-Clinically Significant
NHLBI	National Heart Lung and Blood Institute
OLE	Open Label Extension
PFT	Pulmonary Function Test
PO	Primary Objective
PP	Per-Protocol

PRO	Patient Reported Outcome
PT	Preferred Term
PVV	Pulmonary Vessel Volume
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SO	Secondary Objective
SOC	System Organ Class
SVC	Slow Vital Capacity
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TLC	Total Lung Capacity
ULN	Upper Limit Normal
US	United States

1 Introduction

This document is the statistical analysis plan (SAP) for the PRM-151-202 study. The purpose of this SAP is to provide a comprehensive and detailed description of the statistical analyses that will be carried out to assess the clinical efficacy and safety of the study treatment, as outlined in the study protocol version 4.0, dated 4 February 2016. The SAP pre-specifies the statistical approaches to be used and is validated prior to the study database lock and the unblinding of the randomisation schedule, to ensure the credibility of the study findings.

2 Highlights from study protocol

2.1 Background/Rationale

Full details of the background and rationale for the study are provided in Section 1 of the protocol.

2.2 Study Objectives

2.2.1 Primary objective (PO)

The primary objective of this study (**PO1**) is to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC [% predicted], pooling subjects on a stable dose of pirfenidone or nintedanib and subjects not on other treatment for IPF.

2.2.2 Secondary objectives (SO)

The secondary objectives of this study are:

- **SO1:** To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on high-resolution CT (HRCT) imaging analysis, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF.
- **SO2:** To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC [% predicted], separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- **SO3:** To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma as quantified on HRCT imaging analysis, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- **SO4:** To assess the tolerability and safety of PRM-151 in subjects with IPF through Week 28.
- **SO5:** To assess the ability of PRM-151 to reduce disease-related events associated with mortality

- **SO6:** To determine the effect size of PRM-151 relative to placebo on pulmonary function in addition to mean change in FVC [% predicted]
- **SO7:** To determine the effect size of PRM-151 relative to placebo on 6 minute walk distance
- **SO8:** To determine the effect size of PRM-151 relative to placebo on DLCO.

2.2.3 Exploratory Objectives (EO)

The exploratory objectives of this study are:

- **EO1:** To evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC [% predicted] and 6 minute walking distance, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF and separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.
- **EO2:** To assess the impact of PRM-151 on disease related symptoms.
- **EO3:** To assess the impact of PRM-151, disease pathogenesis and disease progression on exploratory serum, cellular and genetic biomarkers
- **E04:** to explore the relationship between PK and select PD parameters

2.3 Investigational plan

2.3.1 Study design and randomisation

This study is a Phase 2, randomized, double-blind, placebo controlled, pilot study designed to evaluate the efficacy and safety of PRM-151 administered through Week 24 to subjects with IPF. Subjects meeting the eligibility criteria for the study will be randomized with a 2:1 ratio to PRM-151 at a dose of 10 mg/kg every 4 weeks or placebo. The randomization will be stratified according to other treatments for IPF (with two strata: patients receiving either pirfenidone or nintedanib and patients with no other treatment for IPF, with a minimum of 25% of patients on no other treatment). Efficacy will be evaluated through pulmonary function tests (PFTs) including spirometry, Diffusion Capacity (DLCO) and Total Lung Capacity by Nitrogen washout method (TLC), quantitative imaging analysis of high resolution CT (HRCT), 6 minute walk test (6MWT), and patient reported outcomes (PROs).

Subjects will be evaluated for study eligibility during Screening within 4 weeks before enrollment and baseline assessments. Subjects who are determined to be eligible, based on screening assessments, will be enrolled in the study and randomly allocated to treatment with PRM-151 or placebo. Subjects will receive study drug treatment for at least 24 weeks.

Approximately 117 subjects will be randomly assigned on a 2:1 basis to treatment with PRM-151 or placebo, as follows:

- PRM-151 10 mg/kg IV infusion over 60 minutes days 1, 3, and 5 of week 0, then one infusion every 4 weeks

- Placebo IV infusion over 60 minutes on days 1, 3, and 5 of week 0, then one infusion every 4 weeks

After completion of study treatment through Week 24, all subjects may receive PRM-151 10 mg/kg IV infusion over 60 minutes Days 1, 3, and 5, then once every 4 weeks for up to an additional 96 weeks in an open label study extension. Dosing on Days 1, 3 and 5 will be repeated once every 24 weeks.

2.3.2 Determination of sample size

The primary objective is not to formally demonstrate the superiority of PRM-151 over placebo, but to provide a reliable estimate of the size of the effect of PRM-151 on absolute change from baseline to 28 weeks in mean FVC [% predicted], hereafter referred to as the primary endpoint. Nevertheless, the sample-size has been calculated to ensure a sufficient power to demonstrate the efficacy of PRM-151 over placebo on the primary endpoint under a set of hypotheses on effect sizes in the two groups and on the variability of the primary endpoint. The primary endpoint will be tested in a model with two types of subjects: subjects on a stable dose of pirfenidone or nintedanib, and subjects not on other treatment for IPF. The sample size calculation is based on the following assumptions:

- Primary endpoint is normally distributed.
- Homogeneity of variance, *i.e.*, the standard deviation is the same in both arms, and for both types of subjects.
- Randomization ratio PRM-151: placebo equals 2:1.
- Expected value of the primary endpoint for subjects on pirfenidone or nintedanib will be -1.5%.
- Expected value of the primary endpoint for subjects on no other treatment will be -3%.
- Expected value of the primary endpoint for subjects on PRM-151 will be $\geq 0.75\%$.
- Standard deviation of the primary endpoint is 5%.
- 75% of subjects will be on a stable dose of pirfenidone or nintedanib.
- 25% of subjects will not be on other treatment for IPF.
- Significance level (α)=0.10 two-sided.
- Desired power to demonstrate superiority is 80%.

A sample size of one hundred and two (102) evaluable subjects in total (68 PRM-151 and 34 placebo) is enough to demonstrate statistical significance at $p<0.10$ two-sided with a power of 80% under the above assumptions. Assuming a non-evaluability rate of about 15%, 117 subjects in total (78 PRM-151 and 39 placebo) are to be enrolled. Stratified randomization will ensure a balance of PRM-151: placebo within patients on pirfenidone or nintedanib and not on any other therapy, with at least 25% of patients on no other therapy.

2.3.3 Study assessments and study plan

Efficacy Assessments

Subjects undergo testing on an every 4 week basis after randomization (occurring at weeks 4, 8, 12, 16, 20, 24 and 28) for efficacy and safety (See Figure 1). For all analysis presented in this SAP we considered W28 as the end of study date. During treatment, PFTs, 6MWT, and PROs will be evaluated on an every 4 week basis. HRCT will be performed on Day 1 as the Baseline assessment and again at the completion of treatment at Week 28. HRCT and PFTs must be done on the same day. PFTs will be reviewed centrally by reviewers blinded to treatment group and time point. This central evaluation of PFTs will be used for the primary analysis of the study.

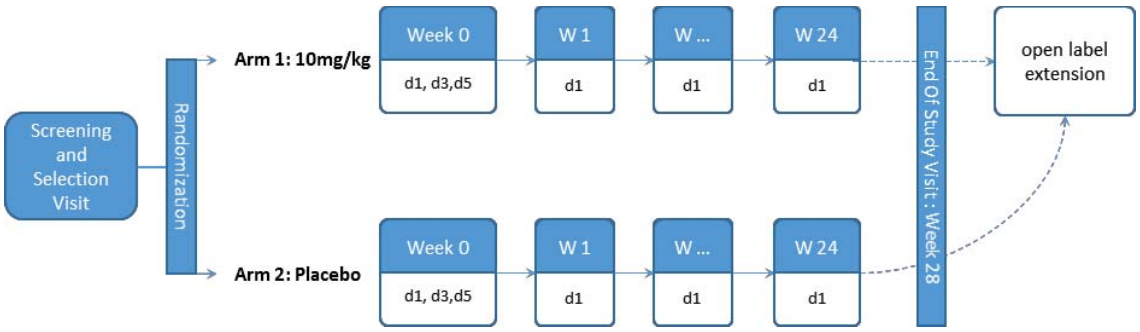

Figure 1: Study Plan

Tolerability/Safety Assessments

Tolerability/Safety will be evaluated over the treatment period (up to week 28) from reported adverse events (AEs), scheduled physical examinations, vital signs, and clinical laboratory test results. Adverse events and concomitant medications will be assessed at all study visits. In addition, information regarding hospitalizations, emergency department visits, and unscheduled or urgent care visits to a health care provider due to a deterioration in respiratory status or symptoms will be collected at all study visits.

Schedule of events

Schedule of events	Screening ≤ 28 days	Treatment Period				Open Label Extension
		Week 0 (± 1 day)		W4, W8, W12, W16, W20, W24 (± 3 days)	W28 (± 3 days)	W28-W128 (± 3 days)
Informed Consent	x					
Demographics	x					
Past Medical History	x					
Inclusion/Exclusion	x	x				
Vital Signs	x	x	x	x	x	x
Physical Exam[1]	x	x		x	x	x
Height (cm)	x					
Weight (kg)	x	x		x		x
Prior/Concomitant Medications	x	x	x	x	x	x
Special list of ecluded medications	x	x	x	x	x	x
AE/SAE Assessment		x	x	x	x	x
ECG & Cytokines (ONLY in the event of an IRR)		x	x	x		
Efficacy Assessment[2]						
Patient Reported Outcomes; K-BILD & LCQ	x	x		x	x	x
Pulmonary Function Tests (PFTs)	x	x		x	x	x
DL_{CO}[3]	x	x			x	x
FRC &TLC by nitrogen washout method[4]	x	x			x	x
HRCT (with spirometry at select sites)[5]		x			x	x
6-minute walk test	x	x		x	x	x
Pregnancy test	x					
Complete Blood Count	x	x		x	x	x
Chemistry, BUN/creatinine	x	x		x	x	x
Coagulation	x	x		x	x	x
Status of baseline genetic characteristics[6]		x				
Anti-pentraxin 2 antibodies (ADA), Pre-dose		x		x	x	x
Pentraxin-2 levels, Pre-dose		x		x	x	x
Exploratory laboratory assessments (optional)[7]		x			x	x
PRM-151 dosing[8]		x	x	x		x

[1]Full physical exam at screening and an abbreviated physical exam thereafter.

[2]PROs should be done first before PFTs and 6MWT and 6MWT should be done last after PROs and PFTs if possible. During open-label extension, subjects will have PROs, PFTs and 6MWT every 4 weeks for the first 24 weeks, then every 12 weeks

[3]Diffusion capacity should be done on the same day as HRCT.

[4]FRC &TLC by nitrogen washout method should be done on the same day as HRCT .

[5]During open-labeled extension, subjects will have DLco and FRC & TLC by nitrogen washout every 12 weeks and HCRT at 1.5 years (W76) and 2.5 years (W128).

[6]TLR3 L412F polymorphism, MUC5B promoter polymorphism

[7] During open label extension, subjects will have optional exploratory labs at Week 128.

[8] Dosing on Days 1, 3, and 5 will be repeated every 24 weeks during the extension.

3 Analysis datasets

3.1 Reasons for excluding patients from analysis datasets

3.1.1 Major protocol deviations

Major protocol deviations are defined as deviations liable to prevent or change the interpretation of the results of the primary efficacy analysis of the study. Thus, a Study Deviation Guidance Document has been prepared (Final version, dated 27July, 2016). Tthis guidance is not exhaustive and will be reviewed at the time of the blind review meeting.

3.1.2 Minor protocol deviations

All deviations will be reviewed and adjudicated as either major or minor during the blind review meeting before database lock and unblinding of the study drug treatment code.

3.1.3 Study treatment discontinuations - Study discontinuations

The Investigator may discontinue study drug treatment prematurely for any of the following reasons:

- Subject, Investigator, or Sponsor request
- Protocol violation
- AE
- Pregnancy
- Progression of disease that, in the opinion of the Investigator, precludes further study drug treatment
- Subject decision: a subject may withdraw consent to participate in the study at any time

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol.

All subjects are required to adhere to the protocol-specified visit schedule. If a subject misses a scheduled visit, attempts should be made to reschedule the visit within the visit windows described above. Failure to attend scheduled study visits may result in discontinuation from the study.

3.2 Primary efficacy dataset: All Treated Set (ATS)

The All Treated Set (ATS) will consists in all randomized patients having received at least one administration of the study medication. The patients will be analyzed in the treatment arm attributed by the randomization process whatever the treatment they actually received ("as randomized" analysis).

The ATS dataset will be used for the for the primary efficacy analyses in this trial.

3.3 Per-protocol (PP) dataset

The Per Protocol (PP) set will comprise of a subset of the ATS analysis population:

- Randomized
- treated with the IMP,
- having received the planned IMP infusions at least for the complete three first cycles
- who did not present any major protocol deviations.
- who have at least one post-cycle 3 evaluation of the primary efficacy criterion (FVC [% predicted])

The PP dataset will be used for secondary analyses of the primary efficacy criterion and for the analysis of some selected secondary efficacy criteria, as described in section 5.2.5.2.

3.4 Safety (SAF) dataset

The safety dataset is defined as all randomized subjects having received at least one dose of study treatment. In the event of subjects having received treatments that differed from those assigned according to the randomisation schedule, then the safety analyses should be conducted according to the treatment actually received (As Treated analysis) rather than according to the randomisation groups.

The SAF dataset will be used to perform the analysis of safety.

4 Endpoints for analysis

4.1 Efficacy endpoints

4.1.1 Primary efficacy endpoint

The primary efficacy endpoint for the study is the mean change from baseline in FVC [% predicted] from Baseline to Week 28. Data for FVC [% predicted] will be provided by BioMedical Systems (BMS) and analysed without any transformation or derivation. The specification on how this variable is measured and computed are provided in the BMS specification document (PRM 151-202 Analysis Plan FINAL Version 1.0 02MAY16).

4.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints for the study are:

- Structural Imaging:
  - Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA) including ground glass density, reticular changes, and honeycombing, using quantitative imaging software.
  - Mean change from Baseline to Week 28 in volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of normal lung (non-ILA), including normal and mild low attenuation areas, using quantitative imaging software.
  - Correlation between mean change from Baseline to Week 28 in FVC [% predicted] and mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA), including ground glass density, reticular changes, and honeycombing by quantitative imaging software.
- FVC [ml and % predicted] based pulmonary function tests:
  - Proportion (%) of subjects with a decline in FVC [% predicted] of ≥ 5% and ≥ 10% from baseline to week 28.
  - Proportion (%) of subjects with a decline in FVC [ml] of ≥ 100ml and ≥ 200ml from baseline to week 28.
  - Proportion of subjects with an increase in FVC [% predicted] of ≥ 5% and ≥10% from baseline to week 28.
  - Proportion of subjects with an increase in FVC [ml] of ≥ 100 ml and ≥ 200 ml from baseline to week 28.
  - Proportion of subjects with stable disease by FVC [% predicted], defined as a change in FVC [% predicted] of < 5% from baseline to week 28.
  - Proportion of subjects with stable disease by FVC in ml, defined as a change in FVC of < 100ml from Baseline to week 28.
- Others pulmonary function tests:

  - Mean change from Baseline to Week 28 in Hb-corrected DLCO *i.e.*, diffusion capacity of carbon monoxide [% predicted].
- Other endpoints
  - Change in 6-minute walk distance [m] from baseline to week 28.

4.1.3 Exploratory efficacy endpoints

There are five types of exploratory endpoints for the study.

The first type is based on the examination of FVC [% predicted, and ml] and 6MWT [m]:

- Change from Baseline at Weeks 4, 8, 12, 16, 20, 24 and 28 for the FVC [% predicted], FVC [ml], and 6MWT distance [m].
- Change in FVC for patient subsets on either a stable dose of (i) pirfenidone or (ii) on a stable dose of nintedanib.

The second type of exploratory endpoints is based on structural imaging:

- Transitions from Baseline to Week 28 between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and mild, moderate, and severe low attenuation areas) by quantitative imaging software, will be analyzed upon further development of methodology to measure transitions.
- Correlation of transitions between categories of lung features by quantitative imaging and changes in FVC [% predicted], will be analyzed upon further development of methodology to measure transitions.
- Correlation of transitions between categories of lung features by quantitative imaging and changes in DLCO, will be analyzed upon further development of methodology to measure transitions.
- Correlation between total lung volume by nitrogen washout and total lung volume by imaging
- Correlation of changes in interstitial lung abnormalities and PROs and 6MWD
- Impact of inspiratory effort on results of HRCT quantitative imaging.
- Pulmonary Vessel Volume.
- Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume), representative of interstitial lung abnormalities (ILA) in patients with SVC breathhold at CT scanning ≥90% of SVC supine (comparing PRM151 vs placebo)

The third group of exploratory endpoint is based on patient reported outcomes:

- Change in Patient Reported Outcomes as measured by
  - King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and
  - Leicester Cough Questionnaire (LCQ) from Baseline to Week 28.

The fourth group of exploratory endpoint is based project investigator assessed outcome :

- Acute exacerbations and time to first reported acute exacerbation

The fifth group of exploratory endpoints is related to the analysis of biomarkers:

- Changes in serum and cellular biomarkers and response according to baseline genetic characteristics: [redacted] analysis may be provided at a later stage than the rest of the analyses, some or all the corresponding data may not be available at the time of the database lock.

Pharmacokinetic endpoints: Pentraxin levels will be assayed at baseline, before each study dose infusion and on Week 28.

In addition to the above exploratory endpoints specified in the protocol, it has been decided to perform a retrospective collection of pre-study pulmonary function tests data and, depending on the completeness and usability of the obtained data, to provide descriptive analyses of pre-study evolution of PFT, and, if feasible, to conduct exploratory analyses on the relationship between this pre-study PFT data, and any change during the study and treatment effect.

4.2 Safety endpoints

Safety will be evaluated from reported adverse events (AEs), respiratory decline events, infusion related reactions, scheduled physical examinations, vital signs, and clinical laboratory test results and concomitant medications.

4.2.1 Adverse events

Adverse events (AE) will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) at the start of the coding activities and will be classified by MedDRA Preferred Term (PT) and System Organ Class (SOC). A Treatment Emergent Adverse Events (TEAE) will be defined as any adverse event that occurs from the time of first study treatment dose administered to the patient until last study visit *i.e.*:

- An AE that was not present prior to receiving the first dose of IMP, or
- An AE that was present prior to receiving the first dose of IMP and increased in intensity after the first IMP administration, or
- An AE that was present prior to receiving the first dose of IMP, with no change in the intensity but with a drug relationship that became related after the first IMP administration.

Tolerability/safety will be assessed over the 28 weeks study period *i.e.*, the analysis will be based on all AEs occurring before first dose of the OLE. The analysis will focus on:

- The incidence of TEAEs
- The incidence of Treatment Emergent Serious Adverse Events (TESAEs)
- The incidence of respiratory TEAEs and TESAEs
- The proportion of subjects discontinuing study drug due to TEAEs
- All-cause mortality
- Mortality due to respiratory deterioration

4.2.2 Respiratory Decline Events

During the 28 week study period respiratory decline events are recorded. Such "respiratory decline" events are defined as follows:

- Unscheduled visits to a healthcare professional for respiratory status deterioration.
- Urgent care visit for respiratory status deterioration.
- Hospitalization due to a worsening or exacerbation of respiratory symptoms.

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

- Acute onset of symptoms (< 30 days in duration)
- New radiographic abnormalities (bilateral ground glass or consolidation on HRCT with no pneumothorax or pleural effusion)
- The absence of an identified infectious etiology by routine clinical practice
- Exclusion of alternative causes by routine clinical practice including:
    a. Left heart failure
    b. Pulmonary embolism
    c. Identifiable cause of acute lung injury

Safety will be assessed based on the incidence of "respiratory decline" and further characterized according to the definitions of IPF-related acute exacerbation.

4.2.3 Infusion related reactions

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.

Infusion related reactions will be classified by MedDRA Preferred Term (PT) and System Organ Class (SOC). Safety will be assess based on the incidence of infusion related reactions.

4.2.4 Laboratory endpoints

During the study the following laboratory variables are recorded:

- **Hematology:** Hemoglobin, Hematocrit, Red Blood Cell, White Blood Cell, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, Platelets.
- **Chemistry**: Sodium, Potassium, Chloride, Glucose, Calcium, AST, ALT, Total Bilirubin, Blood Urea Nitrogen, Bicarbonate, Albumin, Creatinine, Alkaline Phosphatase, Total Protein.
- **Coagulation:** Prothrombin Time, Partial Thromboplastin Time, International Normalized Ratio.

Each laboratory result will be categorized in 3 classes of abnormalities according to (see section 8):

- Normal
- Abnormal NCS
- Abnormal CS

Biological safety will be assessed based on raw test results and change from baseline in raw and categorized laboratory results.

4.2.5 Physical Exams

A complete physical examination is performed during screening and an abbreviated physical exam thereafter. A complete physical examinations will include a review of the following body systems:General appearance, Head, Eyes, Ears, Nose, and Throat, Respiratory, Cardiovascular, Abdomen, Neurologic, Extremities and Dermatologic. Safety will be assessed based on abnormalities (normal, abnormal NCS, abnormal CS) in these body systems.

4.2.6 Vital signs

Vital signs, including Weight, Height, BMI, Heart rate, Respiratory rate, Oxygen saturation, Systolic blood pressure, Diastolic bold pressure are measured in the sitting position at each visit. Vital signs will be assessed based on both raw values and change from baseline to each visit in vital signs measurements. Safety will also be assessed based on abnormalities (normal, abnormal) in vital signs.

4.2.7 Concomitant medication

Concomitant medications will be coded according to the latest available version of the WHO-Drug dictionary and tabulated according to the ATC classification.

5 Statistical and Analytical Methods

5.1 General considerations

The statistical analyses are performed in accordance with the ICH E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated. All available efficacy and safety data (according to definition provided in section 4) collected during the randomized phase of the study will be included in data listings and tabulations (i.e., OLE data will not be presented). Except for the analysis of the primary endpoint (see section 5.2.5.1 Primary efficacy analyses) and for selected secondary endpoints (see section 5.2.5.2 for details), all other analyses will be based on observed data only i.e., no missing data will be imputed.
The statistical analyses will be performed by an external Contract Research Organization (CRO), Venn Life Sciences, under the responsibility of the Sponsor.

5.1.1 Presentation of results

The following statistics will be presented:

- For quantitative variables: number of available data, number of missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum values. When relevant, confidence intervals will be calculated for the mean (Student CI) or the median (Hahn & Meeker 1991).
- For qualitative variables: number of available data, number of missing values number and percentage of observations in each category of the variable. Except if otherwise specified, percentages will be calculated using the number of available data as denominator (*i.e.*, not including missing values). When relevant, confidence intervals of proportions will be calculated using the Clopper-Pearson method (Clopper & Pearson 1934).

5.1.2 Significance testing and estimation

For the primary efficacy analysis (see Section 5.2.5.1), the overall type-one error rate will be set to 0.10 two sided. There will be one single primary efficacy analysis, from which the conclusions on efficacy will be drawn. Consequently, there is no issue of multiplicity of primary analyses and no need to adjust the significance level.

For secondary and exploratory endpoint analyses, 90% CIs will be computed. P-values will also be computed for key secondary efficacy endpoints. No adjustment of the type-one error rate will be conducted. As a consequence, the results of these tests will have to be interpreted bearing in mind the issue of multiplicity and the increased risk of erroneously obtaining statistically significant results.

For all fitted models (*i.e.*, Linear Models and Linear Mixed Models), the underlying model assumptions (e.g., homoscedasticity, linearity, independence) and the goodness of fit will be check graphically.

Missing values will not be imputed for exploratory analyses. Consequently, for all model involving 'Time' effect, the 'Time' variable will be treated as a continuous variable. However, if the analysis of the residuals of a given model suggests departures from the underlying model assumptions, it will be re-fitted considering 'Time' as a categorial variable (8 modalities) in order to explore non-linear trend in response variable.

5.2 Planned analysis

5.2.1 Demographics and baseline characteristics

The following demographics variables will be summarised by treatment group on the ATS, SAF and the PP analysis data sets (Statistical tables 14.1.1 to 14.1.3):

- Gender
- Age
- Ethnicity / Race
- Number of years since diagnosis of IPF

The following baseline characteristics will be summarised by treatment group on the ATS analysis data set:

- Vital signs (including Weight and Height) at baseline by treatment group (Statistical table 14.1.2)
- Physical exam at baseline by treatment group (Statistical table 14.1.3)
- Haematology at baseline by treatment group (Statistical table 14.1.4)
- Haematology abnormalities at baseline by treatment group (Statistical table 14.1.5)
- Chemistry at baseline by treatment group (Statistical table 14.1.6)
- Chemistry abnormalities at baseline by treatment group (Statistical table 14.1.7)
- Coagulation at baseline by treatment group (Statistical table 14.1.8)
- Coagulation abnormalities at baseline by treatment group (Statistical table 14.1.9)
- Background therapy - Use of nintedanib and pirfenidone prior to baseline (Statistical table 14.1.10)

The following baseline characteristics will be summarised by treatment group on the ATS and the PP analysis data sets:

- King's Brief interstitial Lung Disease (Statistical table 14.1.11.1.1 to 14.1.11.1.2) and Leicester Cough Questionnaire (Statistical table 14.1.11.2.1 to 14.1.11.2.2) results at baseline by treatment group.
- High Resolution Computed Tomography measurements at baseline by treatment group (Statistical table 14.1.12.1 to 14.1.12.2)
- Pulmonary Function Tests at baseline by treatment group (Statistical table 14.1.13.1 to 14.1.13.2)
- Six-minute Walk Test distance at baseline by treatment group (Statistical table 14.1.1 to 14.1.2)
- Pentraxin-2 levels at baseline by treatment group (Statistical table 14.1.15.1 to 14.1.15.2)

The following baseline characteristics will be summarised by treatment group on the SAF, the ATS and the PP analysis set:

- Anti-Pentraxin 2 antibodies (ADA) at baseline by treatment group (Statistical table 14.1.16.1 to 14.1.16.3)
- Baseline Genetic Status by treatment group (Statistical table 14.1.17.1 to 14.1.17.3)
- Biomarker levels at baseline by treatment group (Statistical table 14.1.18.1 to 14.1.18.3)

All demographics variables and genetic characteristics of each patient (when available for analysis) will be reported in listing 16.2.4.1 and 16.2.4.2 respectively.

5.2.2 Patient disposition and study discontinuations

Patient disposition will be described using a table (Statistical table 14.1.19) and a flow chart (Figure 14.1). The following variables will be tabulated :

- Number of randomised patients, total and per treatment group
- Number of randomised patient by visit, total and per treatment group
- Number of randomised patients who completed the study treatment as planned (until the 7th cycle on week 24), total and by treatment group
- Number of randomised patients who prematurely discontinued the study treatment (before the 7th cycle on week 24), total and by treatment group
- Number of randomised patients who prematurely discontinued the study treatment before completing the first three cycles and/or who do not have at least one post-cycle 3 evaluation of the primary efficacy criterion (FVC [% predicted])
- Number of randomised patients withdrawn from the study (before week 28) total and by treatment group

The numbers of patient within each dataset (ATS, PP and SAF), globally and by treatment group, will be provided (Statistical table 14.1.20, Listing 16.2.3.1) along with reasons for exclusion from the ATS and PP populations (Statistical table 14.1.21 and 14.1.22 respectively). Reasons for exclusions from the ATS and PP populations will also be provided in Listing 16.2.3.2, according to ICHE3.

A breakdown of the reasons for study discontinuations (Statistical Table 14.1.23 will be tabulated by treatment group. All reasons for study discontinuations will be provided in Listing 16.2.1.

All protocol deviations classified during the blinded review meeting according to definitions provided in section 3.1.1 (Major deviations) and 3.1.2 (Minor deviations) will be tabulated by treatment group for the ATS (Statistical table 14.1.24 and 14.1.25 respectively). All major and minor protocol deviations will also be provided in Listing 16.2.2, according to ICHE3.

5.2.3 Medical history – Previous and concomitant therapy

All medication will be coded according to the latest available version of the WHO-Drug dictionary at the start of the coding activities. For the study of medical histories/therapy for IPF we will distinguish the one ended before baseline from the ones still present at baseline. More specifically, the following variables will be summarised for the ATS and the SAF analysis data sets:

- Past medical history by treatment group (Statistical table 14.1.26.1 to 14.1.26.2)
- Current medical history by treatment group (Statistical table 14.1.27.1 to 14.1.27.2)
- Previous therapy for IPF by treatment group (Statistical table 14.1.28.1 to 14.1.28.2)
- Current therapy for IPF by treatment group, with information on dose of pirfenidone/nintedanib (Statistical table 14.1.29.1 to 14.1.29.2)
- Previous other therapy by treatment group (Statistical table 14.1.30.1 to 14.1.30.2)
- Current other therapy (Statistical table 14.1.31.1 to 14.1.31.2)

Medical history as well as previous and concomitant therapy for each patient will be respectively reported in Listings 16.2.4.3. and 16.2.4.4.

5.2.4 Extent of exposure and compliance

Compliance with study treatment will be computed for each subject of the ATS and the PP populations as the proportion of the prescribed IMP that has been actually administered (see section 8). Treatment compliance will then be analyzed globally and by treatment group, as a numerical variable as well as a categorical variable (see section 8, Statistical table 14.1.32.1 to 14.1.32.2).

To analyse the extent of exposure the following variables will be summarised by treatment group for the SAF population (Statistical table 14.3.1):

- number of infusions received
- cumulative volume of IP actually infused
- duration (number of days) between first IP administration and last IP administration

The extent of exposure will also be assessed based on Pentraxin-2 levels. Descriptive statistics for raw values at each visit and for changes from baseline to each visit in Pentraxin-2 levels will be computed by treatment group. This analysis will be performed on both the ATS and the PP dataset (Statistical table 14.3.2.1 to 14.3.2.3, Figures 14.3.1.1 to 14.3.1.2). Individual measurements of Pentraxin-2 levels will be reported in Listing 16.2.6.7.

5.2.5 Efficacy Analysis

5.2.5.1 Primary endpoint analysis

Primary efficacy analysis

Descriptive statistics for (i) raw values at each time point and (ii) change from baseline to each time point in FVC [% predicted] will be computed by treatment group for the ATS analysis dataset (Statistical tables 14.2.1.1.1 and 14.2.1.2.1). The time variation in FVC [% predicted] will be modelled using a linear mixed effect model with random intercept, with raw values at each time point (from Week 4 to Week 28 included) in FVC [% predicted] as dependent variable (outcome), and stratum, treatment, time (continuous variable calculated as the actual number of days since baseline) and treatment by time interaction as explanatory variables (Statistical table 14.2.1.3.1).

The following statistical hypotheses will be tested:

- H0: Absence of difference between the treatment groups.
- H1: A difference exists between the treatment groups.

Least square means for FVC [% predicted] at each time-point (Statistical table 14.2.1.3.1, Figure 14.2.1.1), estimate of slopes, together with their 2-sided 90 and 95% confidence intervals will be presented for both treatment groups.
The comparison of PRM-151 with placebo will be carried out by

1. computing the estimate (estimate statement from SAS Proc MIXED) of the between group difference in change from baseline at week 28,
2. computing the corresponding 90% confidence interval
3. computing the p-value of the difference estimate compared to 0.

Statistical significance will be determined using a 2-sided type-one error rate of 0.10.
The listing of the estimates of the random parameters will be provided (Listing 16.2.6.9.1)

Due to the number of sites planned to recruit and randomize patients in the study, it is expected that each site will include too few patients to allow the inclusion of study site as a covariate in the analysis.

Sensitivity efficacy analysis on the Full Analysis Set population

To assess the effect of including or excluding patient without any post-baseline efficacy measurement from the primary efficacy analysis population (ATS), the primary efficacy analysis described above will be repeated on the Full analysis set population (initially planned in the protocol as the primary efficacy population) and defined as all randomized patients having received at least one administration of the study medication with a baseline and at least one post-baseline assessment of FVC [% predicted] (primary efficacy criterion) available (Statistical tables 14.2.1.1.3, 14.2.1.2.3 and 14.2.1.3.3, Figure 14.2.1.3)

Sensitivity efficacy analysis on the ATS dataset

The primary efficacy analysis as described above will be repeated with addition of descriptive statistics by stratum, and of the treatment by stratum by time interaction,together with the three two by two interactions, terms in the analysis model (Statistical tables 14.2.2.1, 14.2.2.2, 14.2.2.3, Figure 14.2.2).

In case of a significant qualitative treatment by stratum by time interaction, the data will be carefully examined searching for a potential explanation and the conclusions of the primary efficacy analysis will have to be interpreted cautiously.

The primary efficacy analysis as described above will be repeated without adjusting on stratum in the analysis model (Statistical table 14.2.3).

Potential differences in treatment effect according to study site will be addressed by tabulating both raw values of FVC [% predicted] and change from baseline to each visit in FVC [% predicted] by site on the ATS (Statistical tables 14.2.4.1.1 and 14.2.4.2.18), but it is expected that due to the small number of patients within each site no precise estimates will be obtained for most of the sites.

Sensitivity efficacy analysis on the PP dataset

The primary efficacy analysis as described above will be repeated on the PP analysis data set (Statistical tables 14.2.1.1.2, 14.2.1.2.2 and 14.2.1.3.2, Figure 14.2.1.2).

Initially planned primary efficacy analysis (ATS and FAS)
The initially planned primary efficacy analysis will be computed on both the FAS and the ATS:
Descriptive statistics for (i) raw values at baseline and week 28 and (ii) for change from baseline to Week 28 in FVC [% predicted] will be computed by treatment group. The mean change from baseline to Week 28 in FVC [% predicted] will be compared between treatment groups using an ANOVA model with treatment group and stratum as explanatory variables. This analysis will use Multiple Imputation relying on monotone regression methods (both efficacy variables including 6MWD, DLCO and other variables such as gender or age can be used in the imputation model) for missing data at week 28. Least square means for changes from baseline to Week 28 in FVC [% predicted], together with their 2-sided 90 and 95% confidence intervals will be presented for each treatment

groups (Statistical table 14.2.5.1.1 and 14.2.5.2.2). The mean difference between the two groups will also be presented with its 2-sided 90 and 95% confidence intervals.

5.2.5.2 Secondary efficacy analyses

For all secondary efficacy endpoints, the analyses will be based on observed data only *i.e.*, no data will be imputed. All the following analyses will be performed on both the ATS and the PP analysis data set.

SO1: *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma (normal + mild LAA) and interstitial lung abnormalities (ILA) as quantified on high-resolution CT (HRCT) imaging analysis, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF.*

HRCT is performed at baseline and W28. Descriptive statistics will be computed by treatment group for baseline, week 28 and change from baseline to Week 28 in total lung volume and volume (in ml and % of total lung volume) of parenchyma features representative of normal lung (normal + mild LAA) and representative of interstitial lung abnormalities (ILA) as quantified by HRCT imaging (see section 8, Statistical table 14.2.6.1.1 and 14.2.6.2.2). A model similar to that of the primary analysis (see section 5.2.5.1) will be used to compare the two groups (Statistical tables 14.2.6.3.1 to 14.2.6.3.2, Figure 14.2.4.1 to 14.2.4.2). Individual's measurement of total lung volume and volume of parenchymal features quantified by HRCT imaging will be reported in Listing 16.2.6.3.

SO2: *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

The same model as the one for the primary analysis (see section 5.2.5.1) will be used for each subgroup (Statistical table 14.2.7.1.1 to 14.2.7.2.2, Figure 14.2.5.1.1 to 14.2.5.2.2). All measurements of FVC [% predicted] will be reported in Listing 16.2.6.1.1.

SO3: *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung (defined as normal + mild LAA) parenchyma and interstitial lung abnormalities* (ILA) *as quantified on HRCT imaging analysis, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

Descriptive statistics will be computed by treatment group and stratification level for week 0, week 28 and change from baseline to Week 28 in total lung volume and volume (in ml and % of total lung volume) of parenchyma features representative of normal (normal + mild LAA) lung and representative of interstitial lung abnormalities (ILA) as quantified by HRCT imaging (see section 8). A model similar to that of the primary analysis (see section 5.2.5.1) will be used to compare the two groups (Statistical table 14.2.8.1.1.1 to 14.2.8.2.3.2, Figure 14.2.6.1.1 to 14.2.6.2.2).

Individual's measurement of total lung volume and volumes of parenchymal features quantified by HRCT imaging will be reported in Listing 16.2.6.3.

SO4: *To assess the tolerability and safety of PRM-151 in subjects with IPF through Week 28.*

See Section 5.2.6 safety analysis.

SO5: *To assess the ability of PRM-151 to reduce disease-related events associated with mortality*

See Section 5.2.6 safety analysis.

SO6: *To determine the effect size of PRM-151 relative to placebo on pulmonary function in addition to mean change in FVC% predicted*

To determine the effect size of PRM-151 relative to placebo on pulmonary function, descriptive qualitative statistics and Odds-Ratios (PRM-151 /Placebo) with their 90% CIs will be calculated by treatment group and stratification level for:

- Subjects with a decline in FVC [% predicted] of ≥ 5% and ≥ 10% from baseline to week 28.
- Subjects with a decline in FVC [ml] of ≥ 100ml and ≥ 200ml from baseline to week 28.
- Subjects with an increase in FVC [% predicted] of ≥ 5% and ≥10% from baseline to week 28.
- Subjects with an increase in FVC [ml] of ≥ 100 ml and ≥ 200 ml from baseline to week 28.
- Subjects with stable disease by FVC [% predicted], defined as a change in FVC [% predicted] of < 5% from baseline to week 28.
- Subjects with stable disease by FVC in ml, defined as a change in FVC [ml] of < 100ml from Baseline to week 28.

For each of these endpoints treatment groups will be compared using the Cochran-Mantel-Haenszel general association test available in the SAS Freq procedure, adjusting for the Stratum effect (Statistical table 14.2.9.1 to 14.2.9.2). Due to the small sample-size, the exact version of the test will be used. Odds ratio (with 90% CI) together with p-values will be reported.

SO7: *To determine the effect size of PRM-151 relative to placebo on 6-minute walking distance*

The same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used (Statistical tables 14.2.10.1.1 to 14.2.10.3.2, Figure 14.2.7.1 to 14.2.7.2). All results of the 6-minute walk test will be reported in Listing 16.2.6.2.

SO8: *To determine the effect size of PRM-151 relative to placebo on DLCO.*

The same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used (Statistical tables 14.2.11.1.1 to 14.2.11.3.2, Figure 14.2.8.1 to 14.2.8.2). All DLCO measurements will be reported in Listing 16.2.6.1.2.

SO9: *To determine the correlation between change in FVC [% predicted] and total lung volume and volume of ILA on HRCT from Baseline to Week 28*

Correlation between change from baseline in FVC[% predicted] and (i) total lung volume (Statistical table 14.2.12.1.1 and 14.2.12.1.2, Figures 14.2.9.1.1 and 14.2.9.1.2) and (ii) volume of ILA on HRCT will be produced along with the corresponding scatter plots (Statistical table 14.2.12.2.1 and 14.2.12.2.2, Figures 14.2.9.2.1 and 14.2.9.2.2).

5.2.5.3 Exploratory efficacy analyses

For all exploratory efficacy endpoints, the analyses will be based on observed data only *i.e.*, no data will be imputed.

EO1: *To evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC % predicted, FVC in ml and 6 minute walking distance, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF and separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

A model similar to that of the primary analysis (see section 5.2.5.1) but with the addition of random slopes will be used to evaluate on both the ATS and the PP data sets the efficacy and estimate, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF and separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF, the size of effect of PRM-151 relative to placebo in time variations in FVC [% predicted] (Statistical tables 14.2.13.1 to 14.2.14.2.2, Figures 14.2.10.1 to 14.2.11.2.2), FVC [ml] (Statistical tables 14.2.15.1 to 14.2.16.2.2, Figures 14.2.12.1 to 14.2.13.2.2) and 6MWD (Statistical tables 14.2.17.1 to 14.18.2.2, Figures 14.2.14.1 to 14.2.15.2.2). The individual slopes and intercepts will be listed (Listings 16.2.6.10 to 16.2.6.12). Statistical inference (90% CI and p-values) on the slope difference between treated and placebo groups will be reported.

EO2: *To assess the impact of PRM-151 on disease related symptoms and quantitative imaging.*

Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features (see section 8) on HRCT (in ml and % of total lung volume), representative of interstitial lung abnormalities (ILA) will be computed, comparing PRM151 *vs.* placebo (separately) in patients with SVC breathhold at CT scanning ≥90% of SVC supine, with a similar approach to the one used

for the primary analysis (statistical tables 14.2.19.1.1.1 to 14.2.19.2.3.2, Figure 14.2.16.1.1 to 14.2.16.2.2).

For all categories of lung features (including PVV), the change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) wil be computed in subjects treated with PRM-151 and placebo, depending on the completeness and usability of the obtained data.

Change in Patient Reported Outcomes will be assessed based on the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and Leicester Cough Questionnaire (LCQ). Descriptive statistics for raw values and change from Baseline to each visit in total score of both questionnaire will be computed by treatment group. Differences between treatment groups in change from baseline to week 28 for total score of each questionnaire will be tested using a similar approach to the one used for the primary ananlysis (see section 5.2.5.1). These analysis will be performed on both the ATS and the PP data sets (Statistical tables 14.2.20.1.1 to 14.2.20.3.2 and 14.2.21.1.1 to 14.2.21.3.2, Figures 14.2.17.1 to 14.2.17.2 and 14.2.18.1 to 14.2.18.2). All results of K-BILD and LCQ will be reported in Listings 16.2.6.4.1 to 14.2.6.4.2.2 and 16.2.6.5.1 to 16.2.6.5.2.2.

For the LCQ, in addition to the above approach, frequency of patients with changes below or above 1.3 (identified as the minimal important difference) will be tabulated by treatment groups at week 4, 8, 12, 16, 20, 24 and 28 (Statistical table 14.2.21.4.1 and 14.2.21.4.2).

Descriptive statistics for raw values at each visit and change from baseline to each visit in anti-Pentraxin-2 antibodies measurements will be computed by treatment group. This analysis will be performed on both the ATS and the PP dataset (Statistical 14.2.22.1.1 to 14.2.22.2.2). Individual measurements of anti-pentraxin-2 antibodies will be reported in Listing 16.2.6.8.

EO3: *To assess the use of quantitative imaging in IPF*

The correlation between baseline FVC [% predicted], DLCO (corrected for Hb, [% predicted]), TLC by nitrogen washout, PROs and 6MWD and total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of ILA by quantitative imaging, as well as change from Baseline to Week 28 in FVC [% predicted], DLCO (corrected for Hb, [% predicted]), TLC by nitrogen washout, PROs and 6MWD and change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of ILA will be computed. This analysis will be performed on both the ATS and the PP dataset (Statistical tables 14.2.23.1.1 yo 14.2.23.1.2).

For all categories of lung features (including PVV) the correlation between (i) change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) and (ii) change from baseline to week 28 in FVC [% predicted] will be computed. This analysis will be performed on both the ATS and the PP dataset (Statistical tables 14.2.23.2.1 yo 14.2.23.2.2).

For all categories of lung features (including PVV) the correlation between (i) change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) and (ii) change from baseline to week 28 in DLCO will be computed. This analysis will be performed on both the ATS and the PP datasets (Statistical table 14.2.23.3.1 yo 14.2.23.3.2).

The impact of inspiratory effort on results of HRCT quantitative imaging will be assessed by (Statistical table 14.2.23.4.1 to 14.2.23.4.2, Figure 14.2.19.1 to 14.2.19.2):
1. Calculating the proportion of patients performing spirometry guided HRCT with a SVC breathhold at CT scanning ≥90% of SVC supine at baseline and at week 28
2.The correlation of SVC breathhold at CT scanning and SVC supine at baseline and at week 28
3.The correlation between (i) baseline Total lung volume by quantitative imaging and (ii) baseline TLC by nitrogen washout, seperately for patients with SVC breathhold at CT scanning ≥90% of SVC supine, and for patients with SVC <90% or not receiving spirometry-guided HRCT.

EO4: *To assess the impact of PRM-151, disease pathogenesis and disease progression on exploratory serum, cellular and genetic biomarkers*

To assess the impact of PRM-151 on exploratory biomarkers, descriptive statistics for change from baseline to week 28 in biomarkers will be computed by treatment group and by baseline genetic status (MUC5B and TLR polymorphism separately). These analysis will be performed on both the ATS and the PP dataset (Statistical table 14.2.24.1 and 14.2.24.2). Individual biomarker values will be reported in Listing 16.2.6.6. All or part of these analyses may be provided at a later stage than the rest of the analyses described in the SAP, might the corresponding data not be available at the time of the database lock. It is currently anticipated that baseline genetic status will be avialable, but biomarkers will not.

Additional exploratory analysis: ADA vs. FVC [% predicted]
The relationship between Anti-Pentraxin 2 antibodies (ADA) presence and level of FVC [% predicted] in time will be studied by modelling the influence of presence/absence (and/or level) of ADA in the repeated measures mixed model used for the primary efficacy analysis (see section 5.2.5.1) and if relevant using non-parametric spline functions. The most parcimonious model will be chosen on the basis of the AIC (Statistical table 14.2.25.1 and 14.2.25.2).

Additional exploratory analysis: Baseline characteristics vs. FVC
If data lend themselves to it, additional exploratory analysis will be done to test for interaction between baseline characteristics (e.g., FVC/DLCO/6MWD) and change in FVC.

Exploratory analysis of PK/PD relationship

Descriptive statistics and correlation will be computed to explore the relationship of Pentraxin-2 levels vs FVC [% predicted]/FVC [ml]/slope of FVC ml at week 24 and 28, and the relationship of

Pentraxin-2 vs other PFTs/PROs/6MWT (Statistical table 14.2.26.1 and 14.2.26.2). If relevant the corresponding scatter plot will be produced.

Exploratory analysis of relationship between Pentraxin-2 levels and ADA
Correlation coefficient between Pentraxin-2 levels and ADA titer at week 28 will be computed (Statistical tables 14.2.27.1 and 14.2.27.2) and a scatterplot prepared (using logarithmic coordinates for titers).

Exploratory analysis of acute exacerbations
Tabulation of each type of acute exacerbations will be produced (Statistical table 14.2.28.1.1 and 14.2.28.1.2). Descriptive statistic and Kaplan-meier curve will be computed by treatment group for time to first reported acute exacerbation (Statistical tables 14.2.28.2.1 and 14.2.28.2.2).

Additional exploratory analysis: FVC [% predicted] separately on pirfenidone and nintedanib
The same model as the one for the primary analysis (see section 5.2.5.1) will be used separately on (i) patient on a stable dose pirfenidone and (ii) patient on a stable dose of nintedanib (Statistical table 14.2.20.1.1 to 14.2.20.2.2).

Additional exploratory analysis: time variation in historic FVC [% predicted; ml] measurements:
The time variations in historic FVC [% predicted] data (see section 8) will be modelled using a linear mixed effect model with random intercept and slope, with available historic FVC measurements for each patient (until baseline, baseline included) as dependent variable (outcome) and time (continuous variable calculated as the actual number of days before baseline) as explanatory variables (Statistical table 14.2.30.1.1 to 14.2.30.1.2, Figure 14.2.21.1.1 to 14.2.21.1.2). This analysis will be repeated using historic FVC [ml] measurement as dependent variable. (Statistical table 14.2.30.2.1 to 14.2.30.2.2, Figure 14.2.21.2.1 to 14.2.21.2.2). All available individual measurements will be provided in Listing 16.2.6.13.

5.2.6 Safety analyses

Safety analysis will be based on the incidence, intensity, and type of adverse events, incidence of respiratory decline, Infusion related reactions, and clinically significant changes in the subject's physical examination, vital signs and clinical laboratory results. Safety variables will be tabulated and presented for all subjects who have received any amount of study medication.

5.2.6.1 Adverse events

Adverse event listings:

AE listings will be presented and sorted by treatment group, subject, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study and will include durat ion of each episode.

The following listings will be produced:

- Listing of Adverse Events (Listing 16.2.7.1): All adverse events for each patient, including the same event on several occasions, giving both preferred term and the original term used by the investigator. The listing will be sorted by site and by treatment group and should include: Patient identifier / Age, race-ethnicity, sex, weight, height / The adverse event (preferred term, reported term) / Duration of the adverse event / Severity (mild, moderate, severe) / Seriousness (serious, non-serious) / Action taken with study drug (dose reduced, treatment interrupted-delayed, treatment permanently discontinued-omitted, none, not applicable) / Outcome (resolved, resolved with sequelae, ongoing, unknown) / Relationship to study drug (not related, possibly related, probably related) / Date of onset or date of clinic visit at which the event was discovered / Timing of onset of the adverse event.

- Listing of Deaths (Listing 16.2.7.2) and Serious Adverse Events containing the same information as above.

Adverse events tabulations:

Tabulation of adverse events will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events (if relevant). The following tables will be produced for the whole SAF population as well as by treatment group:

Summary of AE (Statistical Table 14.3.3):

- Any AE
- Any TEAE
- Any TEAE leading to permanent study treatment discontinuation
- Any TEAE leading to study discontinuation
- Any TEAE of severe intensity
- Any possibly or probably related TEAE
- Any SAE
- Any TESAE
- Any TESAE leading to study treatment permanent discontinuation
- Any TESAE leading to study discontinuation (optional)
- Any TESAE considered related to the study treatment
- Deaths (if any)
-

Detailed Tables on TEAEs:

- All TEAE by SOC and PT (Statistical Table 14.3.4.1)
- Most frequent TEAEs by SOC and PT and decreasing frequency (Statistical Table 14.3.4.2)
- All possibly or probably related TEAEs by SOC and PT (Statistical Table 14.3.4.3)
- All TEAE by SOC, PT and intensity (Statistical Table 14.3.4.4)

- All TEAE leading to permanent study drug discontinuation by SOC and PT (Statistical Table 14.3.4.5, only produced if more than 5 events)
- All TEAE leading to permanent study discontinuation by SOC and PT (Statistical Table 14.3.4.6, only produced if more than 5 events)

Detailed Tables on TESAEs:

- Any TESAE by SOC and PT (Statistical Table 14.3.5.1)
- All possibly or probably related TESAEs by SOC and PT (Statistical Table 14.3.5.2, only produced if more than 5 events)
- All TESAE by SOC, PT and intensity (Statistical Table 14.3.5.3)
- All TESAE leading to permanent study drug discontinuation by SOC and PT (Statistical Table 14.3.5.4, only produced if more than 5 events)
- All TESAE leading to permanent study discontinuation by SOC and PT (Statistical Table 14.3.5.5, only produced if more than 5 events)
- Death: all causes of mortality and mortality due to respiratory declines (Statistical Table 14.3.5.6)

5.2.6.2 Respiratory decline events

Tabulation of respiratory decline events will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events. The following tables will be produced for the whole SAF population as well as by treatment group:

- All respiratory decline events by PT (Statistical tables 14.3.6.1)
- All respiratory decline events by PT and intensity (Statistical tables 14.3.6.2)
- All respiratory decline events by PT and seriousness (Statistical tables 14.3.6.3)

5.2.6.3 Infusion related reactions

Tabulation of infusion related reactions will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events. The following tables will be produced for the whole SAF population as well as by treatment group:

- All infusion related reactions by PT (Statistical tables 14.3.7.1.1)
- All infusion related reactions by PT and intensity (Statistical tables 14.3.7.1.2)
- All infusion related reactions by PT and seriousness (Statistical tables 14.3.7.1.3)

The potential influence of Anti-Pentraxin 2 antibodies (ADA) and occurrence of IRR will be studied by producing the same tables as described above breaking down the patients according to presence/absence of ADA (Statistical tables 14.3.7.2.1, 14.3.7.2.2 and 14.3.7.2.3).

5.2.6.4 Laboratory safety variables

Table of laboratory safety variables:

Laboratory evaluations will be summarized by visit and by treatment group on the SAF population. For each hematology, chemistry and coagulation variables we will compute:

- Quantitative descriptive statistics on both raw values and change from baseline (Statistical tables 14.3.8.1-2, 14.3.9.1-2 and 14.3.10.1-2)
- Qualitative descriptive statistics (individual patient changes):
    - Number of patients with values: normal, abnormal NCS, abnormal CS (Statistical table 14.3.8.2, 14.3.9.2 and 14.3.10.3)
    - Shift Tables from baseline to each visit (Statistical table 14.3.8.3, 14.3.9.3 and 14.3.10.3)

Depending of their number the clinically significant laboratory abnormalities will not be tabulated but rather presented in individual data listings (Listings 16.2.8.1 to 16.2.8.4).

Figures on laboratory safety variables:

All individual values of a given laboratory measurement for each patient will be produced. When available, the LLN and ULN will be displayed on the graph. Figures will be produced for all hematologic, chemistry and coagulation variables (Figures 14.3.2).

To facilitate the exploration of potential Drug-Induced Liver Injury (DILI), eDISH (Evaluation of Drug-Induced Serious Hepatotoxicity) plots, plotting peak total bilirubin level versus peak ALT level, both expressed as multiples of the upper limit of normal on a base 10 logarithmic scale, together with mlines identifying the normal range and 2 times the upper lipit of the normal range for total bilirubin and three times the upper limit of the normal range for ALT, will be presented (Figure 14.3.3).

Listing of laboratory safety variables:

Listings of all safety-related laboratory test including pregnancy test (Listings 16.2.8.1 to 16.2.8.4) will be prepared, presenting patient id, identification of time point, age, sex, race-ethnicity, weight, identification of laboratory test, raw result, evaluation (normal, abnormal…), investigator judgment on clinical significance on abnormal values. This listing will be presented by treatment group.

5.2.6.5 Physical exams

For all the variables collected during physical examinations at baseline, the frequencies of normal, abnormal NCS and abnormal CS values will be reported by treatment group (Statistical table

14.3.11). All individual measurements collected at baseline and during the subsequent visits will be provided in Listing 16.2.9.1.

5.2.6.6 Vital signs

- Quantitative descriptive statistics: mean, median, standard deviation, min, max based on raw values and change from baseline (Statistical tables 14.3.12.1 and 14.3.12.2)
- Qualitative descriptive statistics (individual patient changes):
    - Proportion of patients with abnormal values (Statistical table 14.3.12.3)
    - Shift Tables presenting the number of patients with normal/abnormal values at baseline and then at each cycle (Statistical table 14.3.12.4)

All individual measurements will be provided in Listing 16.2.9.2.

5.2.6.7 Concomitant medication

Two tables with the proportions of subjects in the SAF population taking each concomitant medication will be provided for:

- Concomitant medications at baseline (started before baseline and stopped after baseline or still ongoing at end of treatment) by treatment group (Statistical table 14.3.13.1).
- Concomitant medications started after baseline by treatment group (Statistical table 14.3.13.2).

Tables summarizing the use of pirfenidone and nintedanib (proportion of patients using each drug) at baseline and started after baseline by treatment group will be prepared on the SAF population (Statistical table 14.3.13.3, 14.3.13.4).

5.3 Statistical/Analytical issues

5.3.1 Adjustments for Covariates

All comparisons of change from baseline to a given visit between treatment groups performed using ANOVA models and pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF, are adjusted for stratification levels.

Analysis of time variation in a given variable using Linear Mixed Models and pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF, are all adjusted for baseline measurements of the response variable and stratification levels.

5.3.2 Handling of Dropouts or Missing Data

Missing data in efficacy analysis:

The statistical model (linear mixed models for repeated measures) used for the primary and most secondary efficacy analyses will be used without imputation of missing values and are valid under the assumption of missingness at random.

Multiple imputation techniques will be used for the sensitivity analysis on the initially planned primary analysis (see Section 5.2.5.1).

All available efficacy and safety data will be included in data listings and tabulations.

Missing or incomplete dates:

For all listings, missing or incomplete dates will be left as they were recorded.

For calculation / sorting / assignation based on dates (*e.g.*, treatment emergent AEs, concomitant medications…), the following rules will apply:

- The most conservative approach will be considered (*i.e.*, if the onset date of an AE/concomitant medication is missing / incomplete, it will be assumed to have occurred during the study treatment phase (*i.e.*, a TEAE for AEs) except when the partial onset date or other available data indicates differently (*e.g.*, start date day missing, but month before the month of baseline date, or stop date before baseline date).
- Medical history or disease diagnosis with missing/incomplete date will be assumed to have occurred before any study treatment except when the partial onset date or other available data indicates differently.
- Assignations based on dates will be reviewed and confirmed or infirmed during the data review meeting
- Missing or partial start or end dates of IMP administration, if any, will be reviewed during the data review meeting.

5.3.3 Interim Analyses and Data Monitoring

No formal interim data analysis is planned for the study.

A blinded DMC will be established to review safety data from this study, thereby better ensuring the safety of study participants. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will be constituted of independent clinicians expert in the field of IPF and clinical research. A formal charter will be established for the conduct of the DMC.

The committee is planned to review the safety data in an unblinded manner, and the efficacy data will be provided semi-blinded by group. However, DMC may request study drug treatment code for group in order to complete their assessment of safety/benefit risk. This request will only be made to the unblinded statistician, as stated in the DMC Charter.

5.3.4 Multicentre studies

This study is planned to be conducted in 18 study sites in 8 countries. Because of the too small expected numbers of patients within sites, all the analysis will be performed on the pooled data over countries and study sites.

5.3.5 Multiple Comparison/Multiplicity

There will be one single primary efficacy analysis, from which the conclusions on efficacy will be drawn. Consequently, there is no issue of multiplicity of primary analyses and no need to adjust the significance level.

5.3.6 Use of an "Efficacy Subset" of Patients

Two efficacy analyses populations are defined, the ATS and the PP. The definition of these populations is available in Section 3. The primary efficacy analysis will be conducted on the ATS. No patient with available post-treatment efficacy data are excluded from the ATS and, consequently from the primary efficacy analysis.

The PP population will be used to conduct a sensitivity analysis and assess the robustness of the primary efficacy analysis conclusions. Any substantial difference between the two analyses will be explored and discussed.
In addition, the SAP planned to conduct the primary analysis on the Full analysis Set. This was then changed to the ATS. Nevertheless, the initially planned analysis on the FAS will be conducted and provided as an additional sensitivity analysis to further assess the robustness of the primary efficacy analysis conclusions and in particular to assess the impact of excluding patient without any post-baseline efficacy measurement from the FASATS population. Any substantial difference with the result obtained for the primary efficacy analysis on the ATS will be explored and discussed.

5.3.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

5.3.8 Examination of Subgroups

Sensitivity analysis of the primary endpoint and some secondary efficacy analyses aim at exploring difference in response variables between the levels of stratification. See sections 5.2.5.1 and 5.2.5.2 for details.

5.4 Data handling conventions

5.4.1 Baseline definitions

For both the efficacy and safety endpoints the last observation prior to the first dose of study treatment administration will be used as the baseline value. This will usually correspond to the measurement performed at day1 week 0 before first-dose. However, in case of missing value at day 1 week 0 the last available value recorded during screening will be used as baseline value.

5.4.2 Retest, Outliers

5.4.2.1 Retests

The retests will be managed as follow:

- Any retest before baseline : the last available value recorded before baseline (day1 week 0) will be used as the baseline
- Any other retest: data will be reviewed and decision will be made during the blind review on the basis of the following rules:
    - Retest on efficacy data: non-missing value the closest to the scheduled visit will be used
    - Retest on safety data: the worst recorded value will be used

5.4.2.2 Outliers

All outlier data will be reviewed during the data review meeting and decisions regarding their use in the statistical analyses will be made.

5.4.3 Unscheduled visits

All unscheduled visit data will be presented in the individual data listings and used in all safety analyses. For categorical results: reallocation to the visit following last infusion. In case of several data the worst observation will be used in tabulation. For numeric results the first value among worst abnormality/grade will be used. These reallocation will be reviewed in blind review meeting.

5.4.4 Visit windowing

The agreement between realized visit date and the expected visit time frame will be reviewed during blind review meeting.

For premature discontinuated patient, all data collected during the End of Study visit will be reallocated to the visit following last infusion.

6 Modifications from the statistical sections in the protocol

6.1 Change in the primary efficacy analysis

According to the protocol, the primary efficacy analysis was to be the Full Analysis Set (FAS), defined as all randomized patients having received at least one administration of the study medication with a baseline and at least one post-baseline assessment of FVC [% predicted] (primary efficacy criterion) available.
Limiting the population to subjects having at least one post-baseline assessment of FVC [% predicted] draws the efficacy population further from the intention to treat paradigm than the exclusion of only untreated patients. Consequently, it has been decided to change the primary efficacy analysis population to the All Treated Set (ATS, see section 3.2) defined as all randomized subjects who have received at least one administration of the investigational medicinal product (IMP).

In addition to this change of population, it has been decided to change the analysis model from the initially planned ANOVA model on change from baseline to week 28 to a linear mixed effect model with random intercept using all measurements available until Week 28 used to compute the estimate of the between group difference in change from baseline at week 28.

6.2 Changes in secondary efficacy analyses

All secondary efficacy analyses will be performed on both the ATS and the PP.

To be consistent with the primary efficacy analysis, the same analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma (normal + mild LAA) and interstitial lung abnormalities (ILA) as quantified on high-resolution CT (HRCT) imaging analysis (SO1).

To be consistent with the primary efficacy ananlysis, the same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF (SO2).

To be consistent with the primary efficacy ananlysis, the same analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in

normal lung (defined as normal + mild LAA) parenchyma and interstitial lung abnormalities (ILA) as quantified on HRCT imaging analysis (SO3).

Odds ratios wil be computed in addition to quantitative statistics to determine (SO6) the effect size of PRM-151 relative to placebo on pulmonary function and mean change in FVC% predicted.

To be consistent with the primary efficacy ananlysis, the same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used to determine the effect size of PRM-151 relative to placebo on 6MWD (SO7) and DLCO (SO8).

6.3 Changes in exploratory efficacy analyses

All exploratory efficacy analysis will be performed on both the ATS and the PP.

It was initially planned (EO1) to evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC % predicted, FVC in ml and 6 minute walking distance using mixed models with random intercepts. To obtain a better decription of individual variability, both random intercepts and random slopes will be used.

The following not initialy planned exploratory analysis were added (see section 5.2.5.3 for details):

- To assess the use of quantitative imaging in IPF (E03)
- To explore the relationship between Anti-Pentraxin 2 antibodies (ADA) presence and level of FVC [% predicted] in time
- To explore PK/PD relationship.
- To explore relationship between Pentraxin-2 levels and ADA
- To explore acute exacerbations
- To explore time variations in FVC % predicted separately in patient (i) on stable dose of pirfenidone and (ii) on a stable dose of pirfenidone.

7 Software documentation

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

8 Derived data

Derived variable	Derivation algorithm
Change from baseline to visit V (continuous)	Change from baseline of variable $X=X_{(Visit\ V)}-X_{(Baseline)}$ o Negative values indicate a decrease in X o Positive values indicate an increase in X

Percent change from baseline to visit V (continuous)	Percent change from baseline of variable X=100 *[$X_{(Visit\ V)}$-$X_{(Baseline)}$]/ $X_{(Baseline)}$ o Negative values indicate a decrease in X o Positive values indicate an increase in X
Treatment compliance	Continuous variable: The compliance C_i for patient *i* will be computed according to: $$C_i = \frac{D_i^t * 100}{D_i^p}$$ where D_i^p mg is the total amount (mg) of IP prescribed to patient *i* and D_i^t is the total amount (mg) of IP actually taken by the patient during the study i.e., before the end of study for patient *i*.
Treatment compliance (categorical)	Categorial variable with three modalities: • $C_i < 80\%$ • $80\% \leq C_i < 120\%$ • $C_i \geq 120\%$
Vital Sign abnormalities	• Heart rate: <50 or >90 • Respiratory rate: <12 or >20 • Body temperature: <36.5°C or >37.5°C • Diastolic Blood Pressure: <60 or >90 • Systolic Blood Pressure: <90 or >140 • Oxygen Saturation: <90
Event Duration	(End Date) – (Start Date) + 1
Total Lung Volume in ml (TLV)	Total lung volume (excluding vessel volume) in ml
Normal Lung Volume in ml (NLV)	NLV=Areas of Normal lung in ml + Mild Low Attenuation Area (LAA) in ml
% of Normal Lung Volume	100 * (NLV in ml) / (TLV in ml)
% of mild Low Attenuation Areas (LAA)	100 * (mild LAA in ml) / (TLV in ml)
% of moderate Low Attenuation Areas (LAA)	100 * (moderate LAA in ml) / (TLV in ml)
% of severe Low Attenuation Areas (LAA)	100 * (severe LAA in ml) / (TLV in ml)
% Ground Glass (GG)	100 * (GG in ml) / (TLV in ml)

% Honeycombing (HC)	100 * (HC in ml) / (TLV in ml)
% Reticular Changes (RC)	100 * (RC in ml) / (TLV in ml)
Interstitial Lung Abnormalities (ILA) in ml	(ILA in ml) = (GG in ml) + (RC in ml) + (HC I ml)
% Interstitial Lung Abnormalities (ILA)	%ILA = %GG + %RC + %HC
Historic FVC (% predicted)	(Historic FVC % predicted) = [Historic FVC (mL)/ Reference Result of FVC (mL) at baseline)]*100

9 Tables, Figures and Listings

9.1 List of tables

n°	Demographics and Baseline
14.1.1 to 14.1.3	Demographics (11.2)
14.1.2	Vital Signs at baseline
14.1.3	Physical examination at baseline
14.1.4	Hematology at baseline
14.1.5	Hematology abnormalities at baseline
14.1.6	Chemistry at baseline
14.1.7	Chemistry abnormalities at baseline
14.1.8	Coagulation at baseline
14.1.9	Coagulation abnormalities at baseline
14.1.10	Background therapy - use of nintedanib and pirfenidone prior to baseline
14.1.11.1.1 to 14.1.11.1.2	K-BILD Questionnaires at baseline
14.1.11.2.1 to 14.1.11.2.2	Leiceister Cough Questionnaires at baseline
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14.1.15.1 to 14.1.15.2	Pentraxin-2 levels at baseline
14.1.16.1 to 14.1.16.3	Anti-Pentraxin 2 antibodies (ADA) at baseline
14.1.17.1 to 14.1.17.3	Baseline Genetic Status
14.1.18.1 to 14.1.18.3	Biomarker levels at baseline
14.1.19	Disposition of patients (10.1)
14.1.20	Datasets analyzed (11.1)
14.1.21	Reasons for exclusion from the ATS
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14.1.23	Reasons for study discontinuations
14.1.24	Major protocol deviations (10.2)
14.1.25	Minor protocol deviations (10.2)
14.1.26.1 to 14.1.26.2	Past medical history
14.1.27.1 to 14.1.27.2	Current medical history

14.1.28.1 to 14.1.28.2	Previous therapy for IPF
14.1.29.1 to 14.1.29.2	Current therapy for IPF
14.1.30.1 to 14.1.30.2	Previous other therapy
14.1.31.1 to 14.1.31.2	Current other therapy
14.1.32.1 to 14.1.32.2	Treatment compliance (11.3)
n°	**Efficacy Results**
14.2.1.1.1 to 14.2.1.1.3	**(PO1) Forced Vital Capacity (% predicted FVC) - raw values at each visit**
14.2.1.2.1 to 14.2.1.2.3	**(PO1) Forced Vital Capacity (% predicted FVC) - change from baseline to each visit**
14.2.1.3.1.a to 14.2.1.3.3.a	**(PO1) Forced Vital Capacity (% predicted FVC): Anova table**
14.2.1.3.1.b to 14.2.1.3.3.b	**(PO1) Forced Vital Capacity (% predicted FVC): Model parameter estimates**
14.2.1.3.1.c to 14.2.1.3.3.c	**(PO1) Forced Vital Capacity (% predicted FVC): Least Square Means by stratum at each visit**
14.2.1.3.1.d to 14.2.1.3.3.d	**(PO1) Forced Vital Capacity (% predicted FVC): Least Square Means for Change from baseline at each visit**
14.2.2.1.a	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - raw values by visit and stratum - No Background Therapy**
14.2.2.1.b	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - raw values by visit and stratum - Pirfenidone or Nintedanib**
14.2.2.2.a	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - change from baseline to each visit by stratum - No Background Therapy**
14.2.2.2.b	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - change from baseline to each visit by stratum - Pirfenidone or Nintedanib**
14.2.2.3.a	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Stratum Interaction - Anova table**
14.2.2.3.b	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Stratum Interaction- Model parameter estimates**
14.2.2.3.c	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Stratum Interaction- Least Square Means by stratum at each visit**
14.2.2.3.d	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Stratum Interaction- Least Square Means by stratum for change from baseline at each visit**
14.2.3.a	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Without adjusting on stratum - Anova table**
14.2.3.b	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Without adjusting on stratum - Model parameter estimates**
14.2.3.c	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Without adjusting on stratum - Least Square Means at each visit**

14.2.3.d	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Without adjusting on stratum - Least Square Means for Change from baseline at each visit**
14.2.4.1.1 to 14.2.4.1.18	**(PO1) Sensitivity analysis: Forced Vital Capacity (% predicted FVC) - raw values at each visit by site**
14.2.4.2.1 to 14.2.4.2.18	**(PO1) Sensitivity analysis: Forced Vital Capacity (% predicted FVC) - change from baseline to each visit by site**
14.2.5.1.1 to 14.2.5.1.2	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Initially planned analysis - Model parameter estimates**
14.2.5.2.1 to 14.2.5.2.2	**(PO1) Sensitivity Analysis: Forced Vital Capacity (% predicted FVC) - Initially planned analysis - Least Square Means by stratum for change from baseline at each visit**
14.2.6.1.1 to 14.2.6.1.2	(SO1) Secondary Efficacy Analysis: HRCT imaging analysis - raw value at each visit
14.2.6.2.1 to 14.2.6.2.2	(SO1) Secondary Efficacy Analysis: HRCT imaging analysis - change from baseline
14.2.6.3.1.a to 14.2.6.3.2.a	(SO1) Secondary Efficacy Analysis: HRCT imaging analysis - Anova table
14.2.6.3.1.b to 14.2.6.3.2.b	(SO1) Secondary Efficacy Analysis: HRCT imaging analysis - Model parameter estimates
14.2.6.3.1.c to 14.2.6.3.2.c	(SO1) Secondary Efficacy Analysis: HRCT imaging analysis - Least Square Means by stratum for change from baseline
14.2.7.1.1.a to 14.2.7.1.2.a	(SO2) Secondary Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Anova table - No Background Therapy
14.2.7.1.1.b to 14.2.7.1.2.b	(SO2) Secondary Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Model parameter estimates - No Background Therapy
14.2.7.1.1.c to 14.2.7.1.2.c	(SO2) Secondary Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Least Square Means at each visit - No Background Therapy
14.2.7.1.1.d to 14.2.7.1.2.d	(SO2) Secondary Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Least Square Means for chage from baseline at each visit - No Background Therapy
14.2.7.2.1.a to 14.2.7.2.2.a	(SO2) Secondary Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Anova table - Pirfenidone or Nintedanib
14.2.7.2.1.b to 14.2.7.2.2.b	(SO2) Secondary Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Model parameter estimates - Pirfenidone or Nintedanib
14.2.7.2.1.c to 14.2.7.2.2.c	(SO2) Secondary Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Least Square Means at each visit - Pirfenidone or Nintedanib
14.2.7.2.1.d to 14.2.7.2.2.d	(SO2) Secondary Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Least Square Means for chage from baseline at each visit - Pirfenidone or Nintedanib
14.2.8.1.1.1 to 14.2.8.1.1.2	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - raw values at each stratum- No Background Therapy
14.2.8.1.2.1 to 14.2.8.1.2.2	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - Change from baseline- No Background Therapy
14.2.8.1.3.1.a to 14.2.8.1.3.2.a	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - Anova table - No Background Therapy

14.2.8.1.3.1.b to 14.2.8.1.3.2.b	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - Model parameter estimates - No Background Therapy
14.2.8.1.3.1.c to 14.2.8.1.3.2.c	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - Least Square Means for change from baseline- No Background Therapy
14.2.8.2.1.1 to 14.2.8.2.1.2	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - raw values at each stratum - Pirfenidone or Nintedanib
14.2.8.2.2.1 to 14.2.8.2.2.2	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - Change from baseline - Pirfenidone or Nintedanib
14.2.8.2.3.1.a to 14.2.8.2.3.2.a	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - Anova table - Pirfenidone or Nintedanib
14.2.8.2.3.1.b to 14.2.8.2.3.2.b	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - Model parameter estimates - Pirfenidone or Nintedanib
14.2.8.2.3.1.c to 14.2.8.2.3.2.c	(SO3) Secondary Efficacy Analysis: HRCT imaging analysis - Separately for each stratum - Least Square Means for change from baseline - Pirfenidone or Nintedanib
14.2.9.1.a to 14.2.9.2.a	(SO6) Secondary analyses: Effect size in PRM-151 - Treatment Effect
14.2.9.1.b to 14.2.9.2.b	(SO6) Secondary analyses: Effect size in PRM-151 - Common Odds Ratio
14.2.10.1.1 to 14.2.10.1.2	(SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - raw values at each visit
14.2.10.2.1 to 14.2.10.2.2	(SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - change from baseline to each visit
14.2.10.3.1a to 14.2.10.3.2a	(SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - Anova table
14.2.10.3.1b to 14.2.10.3.2b	(SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - Model parameter estimates
14.2.10.3.1c to 14.2.10.3.2c	(SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - Least Square Means by stratum at each visit
14.2.10.3.1d to 14.2.10.3.2d	(SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - Least Square Means for Change from baseline at each visit
14.2.11.1.1 to 14.2.11.1.2	(SO8) Secondary Efficacy Analysis: DLCO - raw values at each visit
14.2.11.2.1 to 14.2.11.2.2	(SO8) Secondary Efficacy Analysis: DLCO - change from baseline
14.2.11.3.1a to 14.2.11.3.2a	(SO8) Secondary Efficacy Analysis: DLCO - Anova table
14.2.11.3.1b to 14.2.11.3.2b	(SO8) Secondary Efficacy Analysis: DLCO - Model parameter estimates
14.2.11.3.1c to 14.2.11.3.2c	(SO8) Secondary Efficacy Analysis: DLCO - Least Square Means by stratum for change from baseline
14.2.12.1.1 to 14.2.12.1.2	(SO9) Secondary Efficacy Analysis: Correlation between Forced Vital Capacity (% predicted FVC) and total lung volume
14.2.12.2.1 to 14.2.12.2.2	(SO9) Secondary Efficacy Analysis: Correlation between Forced Vital Capacity (% predicted FVC) and volume of ILA on HRCT
14.2.13.1.a to 14.2.13.2.a	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis - Anova table
14.2.13.1.b to 14.2.13.2.b	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis- Model parameter estimates

14.2.13.1.c to 14.2.13.2.c	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis- Least Square Means by stratum at each visit
14.2.13.1.d to 14.2.13.2.d	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis- Least Square Means for change from baseline at each visit
14.2.14.1.1.a to 14.2.14.1.2.a	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Anova table - No Background Therapy
14.2.14.1.1.b to 14.2.14.1.2.b	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Model parameter estimates - No Background Therapy
14.2.14.1.1.c to 14.2.14.1.2.c	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Least Square Means at each visit - No Background Therapy
14.2.14.1.1.d to 14.2.14.1.2.d	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - No Background Therapy
14.2.14.2.1.a to 14.2.14.2.2.a	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Anova table - Pirfenidone or Nintedanib
14.2.14.2.1.b to 14.2.14.2.2.b	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Model parameter estimates - Pirfenidone or Nintedanib
14.2.14.2.1.c to 14.2.14.2.2.c	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Least Square Means at each visit- Pirfenidone or Nintedanib
14.2.14.2.1.d to 14.2.14.2.2.d	(EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - Pirfenidone or Nintedanib
14.2.15.1.1 to 14.2.15.1.2	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis - Raw Values at Each Visit
14.2.15.1.2 to 14.2.15.2.2	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis - Change from baseline at each visit
14.2.15.3.1.a to 14.2.15.3.2.a	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis - Anova table
14.2.15.3.1.b to 14.2.15.3.2.b	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis- Model parameter estimates
14.2.15.3.1.c to 14.2.15.3.2.c	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis- Least Square Means by stratum at each visit
14.2.15.3.1.d to 14.2.15.3.2.d	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis- Least Square Means for change from baseline at each visit
14.2.16.1.1.1 to 14.2.16.1.1.2	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Raw values at each visit - No Background Therapy
14.2.16.1.2.1 to 14.2.16.1.2.2	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Change from baseline to eah visit - No Background Therapy
14.2.16.1.3.1.a to 14.2.16.1.3.2.a	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Anova table - No Background Therapy
14.2.16.1.3.1.b to 14.2.16.1.3.2.b	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Model parameter estimates - No Background Therapy
14.2.16.1.3.1.c to 14.2.16.1.3.2.c	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Least Square Means at each visit - No Background Therapy
14.2.16.1.3.1.d to 14.2.16.1.3.2.d	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - No Background Therapy

14.2.16.2.1.1 to 14.2.16.2.1.2	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Raw values at each visit - Pirfenidone or Nintedanib
14.2.16.2.2.1 to 14.2.16.2.2.2	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Change from baseline to each visit - Pirfenidone or Nintedanib
14.2.16.2.3.1.a to 14.2.16.2.3.2.a	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Anova table - Pirfenidone or Nintedanib
14.2.16.2.3.1.b to 14.2.16.2.3.2.b	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Model parameter estimates - Pirfenidone or Nintedanib
14.2.16.2.3.1.c to 14.2.16.2.3.2.c	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Least Square Means at each visit- Pirfenidone or Nintedanib
14.2.16.2.3.1.d to 14.2.16.2.3.2.d	(EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - Pirfenidone or Nintedanib
14.2.17.1.a to 14.2.17.2.a	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis - Anova table
14.2.17.1.b to 14.2.17.2.b	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis- Model parameter estimates
14.2.17.1.c to 14.2.17.2.c	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis- Least Square Means by stratum at each visit
14.2.17.1.d to 14.2.17.2.d	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis- Least Square Means for change from baseline at each visit
14.2.18.1.1.1 to 14.2.18.1.1.2	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Raw values at each visit - No Background Therapy
14.2.18.1.2.1 to 14.2.18.1.2.2	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Change from Baseline to each visit - No Background Therapy
14.2.18.1.3.1.a to 14.2.18.1.3.2.a	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Anova table - No Background Therapy
14.2.18.1.3.1.b to 14.2.18.1.3.2.b	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Model parameter estimates - No Background Therapy
14.2.18.1.3.1.c to 14.2.18.1.3.2.c	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Least Square Means at each visit - No Background Therapy
14.2.18.1.3.1.d to 14.2.18.1.3.2.d	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - No Background Therapy
14.2.18.2.1.1 to 14.2.18.2.1.2	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Raw values at each visit - Pirfenidone or Nintedanib
14.2.18.2.2.1 to 14.2.18.2.2.2	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Change from baseline at each visit - Pirfenidone or Nintedanib
14.2.18.2.3.1.a to 14.2.18.2.3.2.a	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Anova table - Pirfenidone or Nintedanib
14.2.18.2.3.1.b to 14.2.18.2.3.2.b	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Model parameter estimates - Pirfenidone or Nintedanib
14.2.18.2.3.1.c to 14.2.18.2.3.2.c	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Least Square Means at each visit- Pirfenidone or Nintedanib

14.2.18.2.3.1.d to 14.2.18.2.3.2.d	(EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - Pirfenidone or Nintedanib
14.2.19.1.1.1 to 14.2.19.1.1.2	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning ≥90% of SVC supine - raw value at each visit
14.2.19.1.2.1.b to 14.2.19.1.2.2	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning ≥90% of SVC supine - change from baseline
14.2.19.1.3.1.a to 14.2.19.1.3.2.a	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning ≥90% of SVC supine - Anova table
14.2.19.1.3.1.b to 14.2.19.1.3.2.b	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning ≥90% of SVC supine - Model parameter estimates
14.2.19.1.3.1.c to 14.2.19.1.3.2.c	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning ≥90% of SVC supine - Least Square Means for change In baseline
14.2.19.2.1.1 to 14.2.19.2.1.2	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning <90% of SVC supine - raw value at each visit
14.2.19.2.2.1.b to 14.2.19.2.2.2	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning <90% of SVC supine - change from baseline
14.2.19.2.3.1.a to 14.2.19.2.3.2.a	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning <90% of SVC supine - Anova table
14.2.19.2.3.1.b to 14.2.19.2.3.2.b	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning <90% of SVC supine - Model parameter estimates
14.2.19.2.3.1.c to 14.2.19.2.3.2.c	(EO2) Exploratory analyses: HRCT image analysis (total lung volume) - SVC breathhold at CT scanning <90% of SVC supine - Least Square Means for change I nbaseline
14.2.20.1.1 to 14.2.20.1.2	(EO2) Exploratory Efficacy Analysis: King's Brief Interstitial Lung Disease Questionnaire (K-BILD) - raw values at each visit
14.2.20.2.1 to 14.2.20.2.2	(EO2) Exploratory Efficacy Analysis: King's Brief Interstitial Lung Disease Questionnaire (K-BILD) - change from baseline to each visit
14.2.20.3.1.a to 14.2.20.3.2.a	(EO2) Exploratory Efficacy Analysis: King's Brief Interstitial Lung Disease Questionnaire (K-BILD) - Anova table
14.2.20.3.1.b to 14.2.20.3.2.b	(EO2) Exploratory Efficacy Analysis: King's Brief Interstitial Lung Disease Questionnaire (K-BILD) - Model parameter estimates
14.2.20.3.1.c to 14.2.20.3.2.c	(EO2) Exploratory Efficacy Analysis: King's Brief Interstitial Lung Disease Questionnaire (K-BILD) - Least Square Means by stratum at each visit
14.2.20.3.1.d to 14.2.20.3.2.d	(EO2) Exploratory Efficacy Analysis: King's Brief Interstitial Lung Disease Questionnaire (K-BILD) - Least Square Means for change from baseline at each visit
14.2.21.1.1 to 14.2.21.1.2	(EO2) Exploratory Efficacy Analysis: Leicester Cough Questionnaire (LCQ) - raw values at each visit
14.2.21.2.1 to 14.2.21.2.2	(EO2) Exploratory Efficacy Analysis: Leicester Cough Questionnaire (LCQ) - change from baseline to each visit
14.2.21.3.1.a to 14.2.21.3.2.a	(EO2) Exploratory Efficacy Analysis: Leicester Cough Questionnaire (LCQ) - Least Square Means
14.2.21.3.1.b to 14.2.21.3.2.b	(EO2) Exploratory Efficacy Analysis: Leicester Cough Questionnaire (LCQ) - Anova table
14.2.21.3.1.c to 14.2.21.3.2.c	(EO2) Exploratory Efficacy Analysis: Leicester Cough Questionnaire (LCQ) - Model parameter estimates

14.2.21.4.1 to 14.2.21.4.2	(EO2) Exploratory Efficacy Analysis: Leicester Cough Questionnaire (LCQ) - frequency of patients with changes below or above 1.3 at each visit
14.2.22.1.1 to 14.2.22.1.2	(EO2) Exploratory Efficacy Analysis: anti-Pentraxin-2 antibodies - raw values at each visit
14.2.22.2.1 to 14.2.22.2.2	(EO2) Exploratory Efficacy Analysis: anti-Pentraxin-2 antibodies - change from baseline to each visit
14.2.23.1.1 to 14.2.23.1.2	(EO3) Exploratory Efficacy Analysis: Use of quantitative imaging in IPF - Baseline correlations
14.2.23.2.1 to 14.2.23.2.2	(EO3) Exploratory Efficacy Analysis: Use of quantitative imaging in IPF - Correlations with change from baseline to week 28 in FVC [%predicted]
14.2.23.3.1 to 14.2.23.3.2	(EO3) Exploratory Efficacy Analysis: Use of quantitative imaging in IPF - Correlations with change from baseline to week 28 in DLCO
14.2.23.4.1 to 14.2.23.4.2	(EO3) Exploratory Efficacy Analysis: Impact of respiratory effort on HRCT quantitative imaging
14.2.24.1.to 14.2.24.2	(EO4) Exploratory analyses: Biomarkers
14.2.25.1.1 to 14.2.25.1.2	(EOA) Additional Exploratory analyses: Influence of ADA on FVC[%predicted] - model selection
14.2.25.2.1 to 14.2.25.2.2	(EOA) Additional Exploratory analyses: Influence of ADA on FVC[%predicted] - model parameter estimates
14.2.26.1 to 14.2.26.2	(EOA) Additional Exploratory analyses: PK/PD relationship
14.2.27.1 to 14.2.27.2	(EOA) Additional Exploratory analyses: Relationship between Pentraxin-2 levels and ADA
14.2.28.1.1 to 14.2.28.1.2	(EOA) Additional Exploratory analyses: Acute exacerbations
14.2.28.2.1 to 14.2.28.2.2	(EOA) Additional Exploratory analyses: Acute exacerbations - Descriptive statistics
14.2.29.1.1.1 to 14.2.29.1.1.2	(EOA) Additional Exploratory Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - raw value at each visit - Nintedanib
14.2.29.1.2.1 to 14.2.29.1.2.2	(EOA) Additional Exploratory Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - change from baseline - Nintedanib
14.2.29.1.3.1.a to 14.2.29.1.3.2.a	(EOA) Additional Exploratory Efficacy Analysis: Forced Vital Capacity (% predicted FVC) - Separately for each stratum - Anova table - Nintedanib
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References

Clopper, C. J., & Pearson, E. S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*, *26*(4), 404-413.

Collard, H. R., Moore, B. B. et al. (2007). Acute exacerbations of idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*, 176(7), 636-643.

Collard, H. R., Yow, E. et al. (2013). Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respiratory research*, 14(1), 73-73.

Hahn, G. J., & Meeker, W. Q. (2011). Statistical intervals: a guide for practitioners (Vol. 328). John Wiley & Sons.