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
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	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 $\geq$ 5% and $\geq$ 10% from Baseline to Week 28.
  - Proportion (%) of subjects with a decline in FVC in ml of $\geq$ 100 ml and $\geq$ 200 ml from Baseline to Week 28.
  - Proportion of subjects with an increase in FVC % predicted of $\geq$ 5% and $\geq$ 10% from Baseline to Week 28.
  - Proportion of subjects with an increase in FVC in ml of $\geq$100 ml and $\geq$ 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.
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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.

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)▮

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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 ($\geq$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 (cm³) 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, 6MWT² 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 $\geq 5\%$ and $\geq 10\%$ 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 $\geq 5\%$ and $\geq 10\%$ 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 28 for 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 $\geq$ 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 ████████████ within 24 hours of discovery either by e-mail or fax to:

- ● ████████████████████
- ● ████████████████████
- ● ██████████████████████████

A completed SAE report is to be sent to ███████ 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 ████████ Drug Safety Unit, immediately but no later than 24 hours of the Investigator's learning of the event to ████████ Safety Unit:

- • ████████████████████
- ● ████████████████████
- ● ██████████████████████████

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 ▮▮▮▮▮▮Safety Unit:

- ▮▮▮▮▮▮▮▮▮▮▮▮▮▮
- ▮▮▮▮▮▮▮▮▮▮▮
- ▮▮▮▮▮▮▮▮▮▮▮▮▮

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 ≥ 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

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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	Baseline Dosing Day 1
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

Assessment																
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] ███

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[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 only 2 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.

PRM-151
Study Protocol PRM-151-202 *Version 4.0*

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 All of the time (continuously)	2 Most times during the day	3 Several times during the day	4 Some times during the day	5 Occasionally through the day	6 Rarely	7 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.