# Statistical Analysis Plan

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

PRM-151-202

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**Versions History**

| Version Number | Date | Detail |
|---|---|---|
| Version 1 | 20 Dec 2016 | Not applicable: First version |
| Version 2 | 08 Jun 2017 | -Updated Tables Figures and Listings list<br>-Added Pulmonary Vessel Volume as Exploratory Endpoint<br>-Added exploratory efficacy analyses of FVC for patient subsets on either a stable dose of (i) pirfenidone or (ii) on a stable dose of nintedanib.<br>-Added exploratory analysis of available historic data of FVC and associated derivation rule.<br>-Added data handling guidance for details regarding data collected at end of study visit for patients prematurely discontinued from the study.<br>-Added derivation rule for variables derived from HRCT data. |

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# Contents

# Abbreviations and definitions

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

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

# 1 Introduction

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

# 2 Highlights from study protocol

## 2.1 Background/Rationale

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

## 2.2 Study Objectives

### *2.2.1 Primary objective (PO)*

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

### *2.2.2 Secondary objectives (SO)*

The secondary objectives of this study are:

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

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

#### *2.2.3 Exploratory Objectives (EO)*

The exploratory objectives of this study are:

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

### 2.3 Investigational plan

#### *2.3.1 Study design and randomisation*

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

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

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

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

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

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

### *2.3.2 Determination of sample size*

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

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

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

### 2.3.3 Study assessments and study plan

*Efficacy Assessments*

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

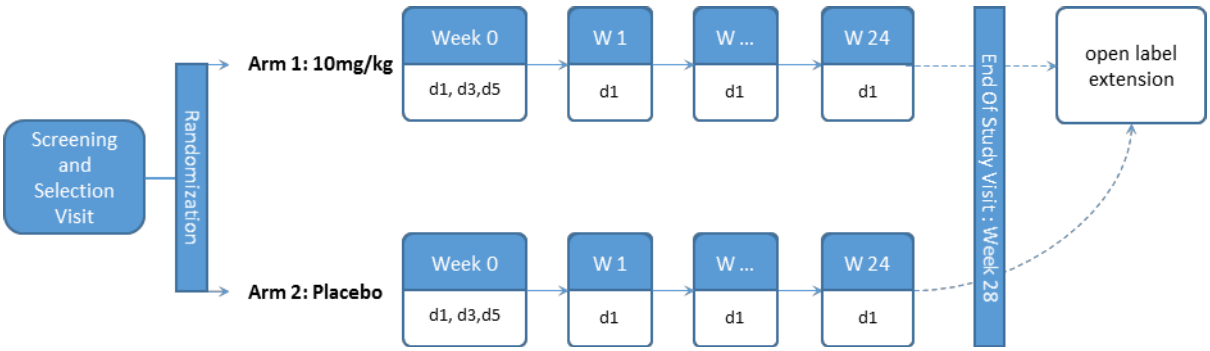


*Figure 1: Study Plan*

*Tolerability/Safety Assessments*

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

*Schedule of events*

| Schedule of events | Screening ≤ 28 days | Treatment Period | | | | Open Label Extension |
|---|---|---|---|---|---|---|
| | | Week 0 (± 1 day) | | W4, W8, W12, W16, W20, W24 (± 3 days) | W28 (± 3 days) | W28-W128 (± 3 days) |
| Informed Consent | x | | | | | |
| Demographics | x | | | | | |
| Past Medical History | x | | | | | |
| Inclusion/Exclusion | x | x | | | | |
| Vital Signs | x | x | x | x | x | x |
| Physical Exam[1] | x | x | | x | x | x |
| Height (cm) | x | | | | | |
| Weight (kg) | x | x | | x | | x |
| Prior/Concomitant Medications | x | x | x | x | x | x |
| Special list of ecluded medications | x | x | x | x | x | x |
| AE/SAE Assessment | | x | x | x | x | x |
| ECG & Cytokines (ONLY in the event of an IRR) | | x | x | x | | |
| **Efficacy Assessment[2]** | | | | | | |
| Patient Reported Outcomes; K-BILD & LCQ | x | x | | x | x | x |
| Pulmonary Function Tests (PFTs) | x | x | | x | x | x |
| $DL_{CO}$[3] | x | x | | | x | x |
| FRC &TLC by nitrogen washout method[4] | x | x | | | x | x |
| HRCT (with spirometry at select sites)[5] | | x | | | x | x |
| 6-minute walk test | x | x | | x | x | x |
| Pregnancy test | x | | | | | |
| Complete Blood Count | x | x | | x | x | x |
| Chemistry, BUN/creatinine | x | x | | x | x | x |
| Coagulation | x | x | | x | x | x |
| Status of baseline genetic characteristics[6] | | x | | | | |
| Anti-pentraxin 2 antibodies (ADA), Pre-dose | | x | | x | x | x |
| Pentraxin-2 levels, Pre-dose | | x | | x | x | x |
| Exploratory laboratory assessments (optional)[7] | | x | | | x | x |
| PRM-151 dosing[8] | | x | x | x | | x |

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

[2]PROs should be done first before PFTs and 6MWT and 6MWT should be done last after PROs and PFTs if possible. During open-label extension, subjects will have PROs, PFTs and 6MWT every 4 weeks for the first 24 weeks, then every 12 weeks

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

[4]FRC &TLC by nitrogen washout method should be done on the same day as HRCT .

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

[6]TLR3 L412F polymorphism, MUC5B promoter polymorphism

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

[8] Dosing on Days 1, 3, and 5 will be repeated every 24 weeks during the extension.

# 3 Analysis datasets

## 3.1 Reasons for excluding patients from analysis datasets

### *3.1.1 Major protocol deviations*

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

### *3.1.2 Minor protocol deviations*

All deviations will be reviewed and adjudicated as either major or minor during the blind review meeting before database lock and unblinding of the study drug treatment code.

### *3.1.3 Study treatment discontinuations - Study discontinuations*

The Investigator may discontinue study drug treatment prematurely for any of the following reasons:

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

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

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

## 3.2 Primary efficacy dataset: All Treated Set (ATS)

The All Treated Set (ATS) will consists in all randomized patients having received at least one administration of the study medication. The patients will be analyzed in the treatment arm attributed by the randomization process whatever the treatment they actually received ("as randomized" analysis).

The ATS dataset will be used for the for the primary efficacy analyses in this trial.

## 3.3 Per-protocol (PP) dataset

The Per Protocol (PP) set will comprise of a subset of the ATS analysis population:

- Randomized
- treated with the IMP,
- having received the planned IMP infusions at least for the complete three first cycles
- who did not present any major protocol deviations.
- who have at least one post-cycle 3 evaluation of the primary efficacy criterion (FVC [% predicted])

The PP dataset will be used for secondary analyses of the primary efficacy criterion and for the analysis of some selected secondary efficacy criteria, as described in section 5.2.5.2.

## 3.4 Safety (SAF) dataset

The safety dataset is defined as all randomized subjects having received at least one dose of study treatment. In the event of subjects having received treatments that differed from those assigned according to the randomisation schedule, then the safety analyses should be conducted according to the treatment actually received (As Treated analysis) rather than according to the randomisation groups.

The SAF dataset will be used to perform the analysis of safety.

# 4 Endpoints for analysis

## 4.1 Efficacy endpoints

### *4.1.1 Primary efficacy endpoint*

The primary efficacy endpoint for the study is the mean change from baseline in FVC [% predicted] from Baseline to Week 28. Data for FVC [% predicted] will be provided by BioMedical Systems (BMS) and analysed without any transformation or derivation. The specification on how this variable is measured and computed are provided in the BMS specification document (PRM 151-202 Analysis Plan FINAL Version 1.0 02MAY16).

### *4.1.2 Secondary efficacy endpoints*

The secondary efficacy endpoints for the study are:

- Structural Imaging:
  - Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA) including ground glass density, reticular changes, and honeycombing, using quantitative imaging software.
  - Mean change from Baseline to Week 28 in volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of normal lung (non-ILA), including normal and mild low attenuation areas, using quantitative imaging software.
  - Correlation between mean change from Baseline to Week 28 in FVC [% predicted] and mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of interstitial lung abnormalities (ILA), including ground glass density, reticular changes, and honeycombing by quantitative imaging software.
- FVC [ml and % predicted] based pulmonary function tests:
  - Proportion (%) of subjects with a decline in FVC [% predicted] of ≥ 5% and ≥ 10% from baseline to week 28.
  - Proportion (%) of subjects with a decline in FVC [ml] of ≥ 100ml and ≥ 200ml from baseline to week 28.
  - Proportion of subjects with an increase in FVC [% predicted] of ≥ 5% and ≥10% from baseline to week 28.
  - Proportion of subjects with an increase in FVC [ml] of ≥ 100 ml and ≥ 200 ml from baseline to week 28.
  - Proportion of subjects with stable disease by FVC [% predicted], defined as a change in FVC [% predicted] of < 5% from baseline to week 28.
  - Proportion of subjects with stable disease by FVC in ml, defined as a change in FVC of < 100ml from Baseline to week 28.
- Others pulmonary function tests:

  - Mean change from Baseline to Week 28 in Hb-corrected DLCO *i.e.*, diffusion capacity of carbon monoxide [% predicted].
- Other endpoints
  - Change in 6-minute walk distance [m] from baseline to week 28.

### *4.1.3 Exploratory efficacy endpoints*

There are five types of exploratory endpoints for the study.

**The first type is based on the examination of FVC [% predicted, and ml] and 6MWT [m]:**

- Change from Baseline at Weeks 4, 8, 12, 16, 20, 24 and 28 for the FVC [% predicted], FVC [ml], and 6MWT distance [m].
- Change in FVC for patient subsets on either a stable dose of (i) pirfenidone or (ii) on a stable dose of nintedanib.

**The second type of exploratory endpoints is based on structural imaging:**

- Transitions from Baseline to Week 28 between all categories of lung features (normal, ground glass density, reticular changes, honeycombing, and mild, moderate, and severe low attenuation areas) by quantitative imaging software, will be analyzed upon further development of methodology to measure transitions.
- Correlation of transitions between categories of lung features by quantitative imaging and changes in FVC [% predicted], will be analyzed upon further development of methodology to measure transitions.
- Correlation of transitions between categories of lung features by quantitative imaging and changes in DLCO, will be analyzed upon further development of methodology to measure transitions.
- Correlation between total lung volume by nitrogen washout and total lung volume by imaging
- Correlation of changes in interstitial lung abnormalities and PROs and 6MWD
- Impact of inspiratory effort on results of HRCT quantitative imaging.
- Pulmonary Vessel Volume.
- Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume), representative of interstitial lung abnormalities (ILA) in patients with SVC breathhold at CT scanning ≥90% of SVC supine (comparing PRM151 vs placebo)

**The third group of exploratory endpoint is based on patient reported outcomes**:

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

**The fourth group of exploratory endpoint is based project investigator assessed outcome** :

- Acute exacerbations and time to first reported acute exacerbation

**The fifth group of exploratory endpoints is related to the analysis of biomarkers:**

- Changes in serum and cellular biomarkers and response according to baseline genetic characteristics: [redacted] analysis may be provided at a later stage than the rest of the analyses, some or all the corresponding data may not be available at the time of the database lock.

**Pharmacokinetic endpoints:** Pentraxin levels will be assayed at baseline, before each study dose infusion and on Week 28.

In addition to the above exploratory endpoints specified in the protocol, it has been decided to perform a retrospective collection of pre-study pulmonary function tests data and, depending on the completeness and usability of the obtained data, to provide descriptive analyses of pre-study evolution of PFT, and, if feasible, to conduct exploratory analyses on the relationship between this pre-study PFT data, and any change during the study and treatment effect.

## 4.2 Safety endpoints

Safety will be evaluated from reported adverse events (AEs), respiratory decline events, infusion related reactions, scheduled physical examinations, vital signs, and clinical laboratory test results and concomitant medications.

### *4.2.1 Adverse events*

Adverse events (AE) will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) at the start of the coding activities and will be classified by MedDRA Preferred Term (PT) and System Organ Class (SOC). A Treatment Emergent Adverse Events (TEAE) will be defined as any adverse event that occurs from the time of first study treatment dose administered to the patient until last study visit *i.e.*:

- An AE that was not present prior to receiving the first dose of IMP, or
- An AE that was present prior to receiving the first dose of IMP and increased in intensity after the first IMP administration, or
- An AE that was present prior to receiving the first dose of IMP, with no change in the intensity but with a drug relationship that became related after the first IMP administration.

Tolerability/safety will be assessed over the 28 weeks study period *i.e.*, the analysis will be based on all AEs occurring before first dose of the OLE. The analysis will focus on:

- The incidence of TEAEs
- The incidence of Treatment Emergent Serious Adverse Events (TESAEs)
- The incidence of respiratory TEAEs and TESAEs
- The proportion of subjects discontinuing study drug due to TEAEs
- All-cause mortality
- Mortality due to respiratory deterioration

### *4.2.2 Respiratory Decline Events*

During the 28 week study period respiratory decline events are recorded. Such "respiratory decline" events are defined as follows:

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

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

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

Safety will be assessed based on the incidence of "respiratory decline" and further characterized according to the definitions of IPF-related acute exacerbation.

### *4.2.3 Infusion related reactions*

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

Infusion related reactions will be classified by MedDRA Preferred Term (PT) and System Organ Class (SOC). Safety will be assess based on the incidence of infusion related reactions.

### *4.2.4 Laboratory endpoints*

During the study the following laboratory variables are recorded:

- **Hematology:** Hemoglobin, Hematocrit, Red Blood Cell, White Blood Cell, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, Platelets.
- **Chemistry**: Sodium, Potassium, Chloride, Glucose, Calcium, AST, ALT, Total Bilirubin, Blood Urea Nitrogen, Bicarbonate, Albumin, Creatinine, Alkaline Phosphatase, Total Protein.
- **Coagulation:** Prothrombin Time, Partial Thromboplastin Time, International Normalized Ratio.

Each laboratory result will be categorized in 3 classes of abnormalities according to (see section 8):

- Normal
- Abnormal NCS
- Abnormal CS

Biological safety will be assessed based on raw test results and change from baseline in raw and categorized laboratory results.

### *4.2.5 Physical Exams*

A complete physical examination is performed during screening and an abbreviated physical exam thereafter. A complete physical examinations will include a review of the following body systems:General appearance, Head, Eyes, Ears, Nose, and Throat, Respiratory, Cardiovascular, Abdomen, Neurologic, Extremities and Dermatologic. Safety will be assessed based on abnormalities (normal, abnormal NCS, abnormal CS) in these body systems.

### *4.2.6 Vital signs*

Vital signs, including Weight, Height, BMI, Heart rate, Respiratory rate, Oxygen saturation, Systolic blood pressure, Diastolic bold pressure are measured in the sitting position at each visit. Vital signs will be assessed based on both raw values and change from baseline to each visit in vital signs measurements. Safety will also be assessed based on abnormalities (normal, abnormal) in vital signs.

#### *4.2.7 Concomitant medication*

Concomitant medications will be coded according to the latest available version of the WHO-Drug dictionary and tabulated according to the ATC classification.

# 5 Statistical and Analytical Methods

## 5.1 General considerations

The statistical analyses are performed in accordance with the ICH E9 guideline and will be based on the pooled data from the individual study sites, unless otherwise stated. All available efficacy and safety data (according to definition provided in section 4) collected during the randomized phase of the study will be included in data listings and tabulations (i.e., OLE data will not be presented). Except for the analysis of the primary endpoint (see section 5.2.5.1 Primary efficacy analyses) and for selected secondary endpoints (see section 5.2.5.2 for details), all other analyses will be based on observed data only i.e., no missing data will be imputed.
The statistical analyses will be performed by an external Contract Research Organization (CRO), Venn Life Sciences, under the responsibility of the Sponsor.

### *5.1.1 Presentation of results*

The following statistics will be presented:

- For quantitative variables: number of available data, number of missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum values. When relevant, confidence intervals will be calculated for the mean (Student CI) or the median (Hahn & Meeker 1991).
- For qualitative variables: number of available data, number of missing values number and percentage of observations in each category of the variable. Except if otherwise specified, percentages will be calculated using the number of available data as denominator (*i.e.*, not including missing values). When relevant, confidence intervals of proportions will be calculated using the Clopper-Pearson method (Clopper & Pearson 1934).

### *5.1.2 Significance testing and estimation*

For the primary efficacy analysis (see Section 5.2.5.1), the overall type-one error rate will be set to 0.10 two sided. There will be one single primary efficacy analysis, from which the conclusions on efficacy will be drawn. Consequently, there is no issue of multiplicity of primary analyses and no need to adjust the significance level.

For secondary and exploratory endpoint analyses, 90% CIs will be computed. P-values will also be computed for key secondary efficacy endpoints. No adjustment of the type-one error rate will be conducted. As a consequence, the results of these tests will have to be interpreted bearing in mind the issue of multiplicity and the increased risk of erroneously obtaining statistically significant results.

For all fitted models (*i.e.*, Linear Models and Linear Mixed Models), the underlying model assumptions (e.g., homoscedasticity, linearity, independence) and the goodness of fit will be check graphically.

Missing values will not be imputed for exploratory analyses. Consequently, for all model involving 'Time' effect, the 'Time' variable will be treated as a continuous variable. However, if the analysis of the residuals of a given model suggests departures from the underlying model assumptions, it will be re-fitted considering 'Time' as a categorial variable (8 modalities) in order to explore non-linear trend in response variable.

## 5.2 Planned analysis

### *5.2.1 Demographics and baseline characteristics*

The following demographics variables will be summarised by treatment group on the ATS, SAF and the PP analysis data sets (Statistical tables 14.1.1 to 14.1.3):

- Gender
- Age
- Ethnicity / Race
- Number of years since diagnosis of IPF

The following baseline characteristics will be summarised by treatment group on the ATS analysis data set:

- Vital signs (including Weight and Height) at baseline by treatment group (Statistical table 14.1.2)
- Physical exam at baseline by treatment group (Statistical table 14.1.3)
- Haematology at baseline by treatment group (Statistical table 14.1.4)
- Haematology abnormalities at baseline by treatment group (Statistical table 14.1.5)
- Chemistry at baseline by treatment group (Statistical table 14.1.6)
- Chemistry abnormalities at baseline by treatment group (Statistical table 14.1.7)
- Coagulation at baseline by treatment group (Statistical table 14.1.8)
- Coagulation abnormalities at baseline by treatment group (Statistical table 14.1.9)
- Background therapy - Use of nintedanib and pirfenidone prior to baseline (Statistical table 14.1.10)

The following baseline characteristics will be summarised by treatment group on the ATS and the PP analysis data sets:

- King's Brief interstitial Lung Disease (Statistical table 14.1.11.1.1 to 14.1.11.1.2) and Leicester Cough Questionnaire (Statistical table 14.1.11.2.1 to 14.1.11.2.2) results at baseline by treatment group.
- High Resolution Computed Tomography measurements at baseline by treatment group (Statistical table 14.1.12.1 to 14.1.12.2)
- Pulmonary Function Tests at baseline by treatment group (Statistical table 14.1.13.1 to 14.1.13.2)
- Six-minute Walk Test distance at baseline by treatment group (Statistical table 14.1.1 to 14.1.2)
- Pentraxin-2 levels at baseline by treatment group (Statistical table 14.1.15.1 to 14.1.15.2)

The following baseline characteristics will be summarised by treatment group on the SAF, the ATS and the PP analysis set:

- Anti-Pentraxin 2 antibodies (ADA) at baseline by treatment group (Statistical table 14.1.16.1 to 14.1.16.3)
- Baseline Genetic Status by treatment group (Statistical table 14.1.17.1 to 14.1.17.3)
- Biomarker levels at baseline by treatment group (Statistical table 14.1.18.1 to 14.1.18.3)

All demographics variables and genetic characteristics of each patient (when available for analysis) will be reported in listing 16.2.4.1 and 16.2.4.2 respectively.

### *5.2.2 Patient disposition and study discontinuations*

Patient disposition will be described using a table (Statistical table 14.1.19) and a flow chart (Figure 14.1). The following variables will be tabulated :

- Number of randomised patients, total and per treatment group
- Number of randomised patient by visit, total and per treatment group
- Number of randomised patients who completed the study treatment as planned (until the 7$^{th}$ cycle on week 24), total and by treatment group
- Number of randomised patients who prematurely discontinued the study treatment (before the 7$^{th}$ cycle on week 24), total and by treatment group
- Number of randomised patients who prematurely discontinued the study treatment before completing the first three cycles and/or who do not have at least one post-cycle 3 evaluation of the primary efficacy criterion (FVC [% predicted])
- Number of randomised patients withdrawn from the study (before week 28) total and by treatment group

The numbers of patient within each dataset (ATS, PP and SAF), globally and by treatment group, will be provided (Statistical table 14.1.20, Listing 16.2.3.1) along with reasons for exclusion from the ATS and PP populations (Statistical table 14.1.21 and 14.1.22 respectively). Reasons for exclusions from the ATS and PP populations will also be provided in Listing 16.2.3.2, according to ICHE3.

A breakdown of the reasons for study discontinuations (Statistical Table 14.1.23 will be tabulated by treatment group. All reasons for study discontinuations will be provided in Listing 16.2.1.

All protocol deviations classified during the blinded review meeting according to definitions provided in section 3.1.1 (Major deviations) and 3.1.2 (Minor deviations) will be tabulated by treatment group for the ATS (Statistical table 14.1.24 and 14.1.25 respectively). All major and minor protocol deviations will also be provided in Listing 16.2.2, according to ICHE3.

### *5.2.3 Medical history – Previous and concomitant therapy*

All medication will be coded according to the latest available version of the WHO-Drug dictionary at the start of the coding activities. For the study of medical histories/therapy for IPF we will distinguish the one ended before baseline from the ones still present at baseline. More specifically, the following variables will be summarised for the ATS and the SAF analysis data sets:

- Past medical history by treatment group (Statistical table 14.1.26.1 to 14.1.26.2)
- Current medical history by treatment group (Statistical table 14.1.27.1 to 14.1.27.2)
- Previous therapy for IPF by treatment group (Statistical table 14.1.28.1 to 14.1.28.2)
- Current therapy for IPF by treatment group, with information on dose of pirfenidone/nintedanib (Statistical table 14.1.29.1 to 14.1.29.2)
- Previous other therapy by treatment group (Statistical table 14.1.30.1 to 14.1.30.2)
- Current other therapy (Statistical table 14.1.31.1 to 14.1.31.2)

Medical history as well as previous and concomitant therapy for each patient will be respectively reported in Listings 16.2.4.3. and 16.2.4.4.

### *5.2.4 Extent of exposure and compliance*

Compliance with study treatment will be computed for each subject of the ATS and the PP populations as the proportion of the prescribed IMP that has been actually administered (see section 8). Treatment compliance will then be analyzed globally and by treatment group, as a numerical variable as well as a categorical variable (see section 8, Statistical table 14.1.32.1 to 14.1.32.2).

To analyse the extent of exposure the following variables will be summarised by treatment group for the SAF population (Statistical table 14.3.1):

- number of infusions received
- cumulative volume of IP actually infused
- duration (number of days) between first IP administration and last IP administration

The extent of exposure will also be assessed based on Pentraxin-2 levels. Descriptive statistics for raw values at each visit and for changes from baseline to each visit in Pentraxin-2 levels will be computed by treatment group. This analysis will be performed on both the ATS and the PP dataset (Statistical table 14.3.2.1 to 14.3.2.3, Figures 14.3.1.1 to 14.3.1.2). Individual measurements of Pentraxin-2 levels will be reported in Listing 16.2.6.7.

### *5.2.5 Efficacy Analysis*

#### 5.2.5.1 Primary endpoint analysis

*Primary efficacy analysis*

Descriptive statistics for (i) raw values at each time point and (ii) change from baseline to each time point in FVC [% predicted] will be computed by treatment group for the ATS analysis dataset (Statistical tables 14.2.1.1.1 and 14.2.1.2.1). The time variation in FVC [% predicted] will be modelled using a linear mixed effect model with random intercept, with raw values at each time point (from Week 4 to Week 28 included) in FVC [% predicted] as dependent variable (outcome), and stratum, treatment, time (continuous variable calculated as the actual number of days since baseline) and treatment by time interaction as explanatory variables (Statistical table 14.2.1.3.1).

The following statistical hypotheses will be tested:

- H0: Absence of difference between the treatment groups.
- H1: A difference exists between the treatment groups.

Least square means for FVC [% predicted] at each time-point (Statistical table 14.2.1.3.1, Figure 14.2.1.1), estimate of slopes, together with their 2-sided 90 and 95% confidence intervals will be presented for both treatment groups.
The comparison of PRM-151 with placebo will be carried out by

1. computing the estimate (estimate statement from SAS Proc MIXED) of the between group difference in change from baseline at week 28,
2. computing the corresponding 90% confidence interval
3. computing the p-value of the difference estimate compared to 0.

Statistical significance will be determined using a 2-sided type-one error rate of 0.10.
The listing of the estimates of the random parameters will be provided (Listing 16.2.6.9.1)

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

*Sensitivity efficacy analysis on the Full Analysis Set population*

To assess the effect of including or excluding patient without any post-baseline efficacy measurement from the primary efficacy analysis population (ATS), the primary efficacy analysis described above will be repeated on the Full analysis set population (initially planned in the protocol as the primary efficacy population) and defined as all randomized patients having received at least one administration of the study medication with a baseline and at least one post-baseline assessment of FVC [% predicted] (primary efficacy criterion) available (Statistical tables 14.2.1.1.3, 14.2.1.2.3 and 14.2.1.3.3, Figure 14.2.1.3)

*Sensitivity efficacy analysis on the ATS dataset*

The primary efficacy analysis as described above will be repeated with addition of descriptive statistics by stratum, and of the treatment by stratum by time interaction,together with the three two by two interactions, terms in the analysis model (Statistical tables 14.2.2.1, 14.2.2.2, 14.2.2.3, Figure 14.2.2).

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

The primary efficacy analysis as described above will be repeated without adjusting on stratum in the analysis model (Statistical table 14.2.3).

Potential differences in treatment effect according to study site will be addressed by tabulating both raw values of FVC [% predicted] and change from baseline to each visit in FVC [% predicted] by site on the ATS (Statistical tables 14.2.4.1.1 and 14.2.4.2.18), but it is expected that due to the small number of patients within each site no precise estimates will be obtained for most of the sites.

*Sensitivity efficacy analysis on the PP dataset*

The primary efficacy analysis as described above will be repeated on the PP analysis data set (Statistical tables 14.2.1.1.2, 14.2.1.2.2 and 14.2.1.3.2, Figure 14.2.1.2).

*Initially planned primary efficacy analysis (ATS and FAS)*
The initially planned primary efficacy analysis will be computed on both the FAS and the ATS:
Descriptive statistics for (i) raw values at baseline and week 28 and (ii) for change from baseline to Week 28 in FVC [% predicted] will be computed by treatment group. The mean change from baseline to Week 28 in FVC [% predicted] will be compared between treatment groups using an ANOVA model with treatment group and stratum as explanatory variables. This analysis will use Multiple Imputation relying on monotone regression methods (both efficacy variables including 6MWD, DLCO and other variables such as gender or age can be used in the imputation model) for missing data at week 28. Least square means for changes from baseline to Week 28 in FVC [% predicted], together with their 2-sided 90 and 95% confidence intervals will be presented for each treatment

groups (Statistical table 14.2.5.1.1 and 14.2.5.2.2). The mean difference between the two groups will also be presented with its 2-sided 90 and 95% confidence intervals.

### 5.2.5.2 Secondary efficacy analyses

For all secondary efficacy endpoints, the analyses will be based on observed data only *i.e.*, no data will be imputed. All the following analyses will be performed on both the ATS and the PP analysis data set.

***SO1:*** *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma (normal + mild LAA) and interstitial lung abnormalities (ILA) as quantified on high-resolution CT (HRCT) imaging analysis, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF.*

HRCT is performed at baseline and W28. Descriptive statistics will be computed by treatment group for baseline, week 28 and change from baseline to Week 28 in total lung volume and volume (in ml and % of total lung volume) of parenchyma features representative of normal lung (normal + mild LAA) and representative of interstitial lung abnormalities (ILA) as quantified by HRCT imaging ( see section 8, Statistical table 14.2.6.1.1 and 14.2.6.2.2). A model similar to that of the primary analysis (see section 5.2.5.1) will be used to compare the two groups (Statistical tables 14.2.6.3.1 to 14.2.6.3.2, Figure 14.2.4.1 to 14.2.4.2). Individual's measurement of total lung volume and volume of parenchymal features quantified by HRCT imaging will be reported in Listing 16.2.6.3.

***SO2:*** *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

The same model as the one for the primary analysis (see section 5.2.5.1) will be used for each subgroup (Statistical table 14.2.7.1.1 to 14.2.7.2.2, Figure 14.2.5.1.1 to 14.2.5.2.2). All measurements of FVC [% predicted] will be reported in Listing 16.2.6.1.1.

***SO3:*** *To determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung (defined as normal + mild LAA) parenchyma and interstitial lung abnormalities* (ILA) *as quantified on HRCT imaging analysis, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

Descriptive statistics will be computed by treatment group and stratification level for week 0, week 28 and change from baseline to Week 28 in total lung volume and volume (in ml and % of total lung volume) of parenchyma features representative of normal (normal + mild LAA) lung and representative of interstitial lung abnormalities (ILA) as quantified by HRCT imaging (see section 8). A model similar to that of the primary analysis (see section 5.2.5.1) will be used to compare the two groups (Statistical table 14.2.8.1.1.1 to 14.2.8.2.3.2, Figure 14.2.6.1.1 to 14.2.6.2.2).

Individual's measurement of total lung volume and volumes of parenchymal features quantified by HRCT imaging will be reported in Listing 16.2.6.3.

**SO4:** *To assess the tolerability and safety of PRM-151 in subjects with IPF through Week 28.*

See Section 5.2.6 safety analysis.

***SO5:*** *To assess the ability of PRM-151 to reduce disease-related events associated with mortality*

See Section 5.2.6 safety analysis.

***SO6:*** *To determine the effect size of PRM-151 relative to placebo on pulmonary function in addition to mean change in FVC% predicted*

To determine the effect size of PRM-151 relative to placebo on pulmonary function, descriptive qualitative statistics and Odds-Ratios (PRM-151 /Placebo) with their 90% CIs will be calculated by treatment group and stratification level for:

- Subjects with a decline in FVC [% predicted] of ≥ 5% and ≥ 10% from baseline to week 28.
- Subjects with a decline in FVC [ml] of ≥ 100ml and ≥ 200ml from baseline to week 28.
- Subjects with an increase in FVC [% predicted] of ≥ 5% and ≥10% from baseline to week 28.
- Subjects with an increase in FVC [ml] of ≥ 100 ml and ≥ 200 ml from baseline to week 28.
- Subjects with stable disease by FVC [% predicted], defined as a change in FVC [% predicted] of < 5% from baseline to week 28.
- Subjects with stable disease by FVC in ml, defined as a change in FVC [ml] of < 100ml from Baseline to week 28.

For each of these endpoints treatment groups will be compared using the Cochran-Mantel-Haenszel general association test available in the SAS Freq procedure, adjusting for the Stratum effect (Statistical table 14.2.9.1 to 14.2.9.2). Due to the small sample-size, the exact version of the test will be used. Odds ratio (with 90% CI) together with p-values will be reported.

***SO7:*** *To determine the effect size of PRM-151 relative to placebo on 6-minute walking distance*

The same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used (Statistical tables 14.2.10.1.1 to 14.2.10.3.2, Figure 14.2.7.1 to 14.2.7.2). All results of the 6-minute walk test will be reported in Listing 16.2.6.2.

***SO8:*** *To determine the effect size of PRM-151 relative to placebo on DLCO.*

The same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used (Statistical tables 14.2.11.1.1 to 14.2.11.3.2, Figure 14.2.8.1 to 14.2.8.2). All DLCO measurements will be reported in Listing 16.2.6.1.2.

***SO9:*** *To determine the correlation between change in FVC [% predicted] and total lung volume and volume of ILA on HRCT from Baseline to Week 28*

Correlation between change from baseline in FVC[% predicted] and (i) total lung volume (Statistical table 14.2.12.1.1 and 14.2.12.1.2, Figures 14.2.9.1.1 and 14.2.9.1.2) and (ii) volume of ILA on HRCT will be produced along with the corresponding scatter plots (Statistical table 14.2.12.2.1 and 14.2.12.2.2, Figures 14.2.9.2.1 and 14.2.9.2.2).

### 5.2.5.3 Exploratory efficacy analyses

For all exploratory efficacy endpoints, the analyses will be based on observed data only *i.e.*, no data will be imputed.

***EO1:*** *To evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC % predicted, FVC in ml and 6 minute walking distance, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF and separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF.*

A model similar to that of the primary analysis (see section 5.2.5.1) but with the addition of random slopes will be used to evaluate on both the ATS and the PP data sets the efficacy and estimate, pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF and separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF, the size of effect of PRM-151 relative to placebo in time variations in FVC [% predicted] (Statistical tables 14.2.13.1 to 14.2.14.2.2, Figures 14.2.10.1 to 14.2.11.2.2), FVC [ml] (Statistical tables 14.2.15.1 to 14.2.16.2.2, Figures 14.2.12.1 to 14.2.13.2.2) and 6MWD (Statistical tables 14.2.17.1 to 14.18.2.2, Figures 14.2.14.1 to 14.2.15.2.2). The individual slopes and intercepts will be listed (Listings 16.2.6.10 to 16.2.6.12). Statistical inference (90% CI and p-values) on the slope difference between treated and placebo groups will be reported.

***EO2:*** *To assess the impact of PRM-151 on disease related symptoms and quantitative imaging.*

Mean change from Baseline to Week 28 in total lung volume and volume of parenchymal features (see section 8) on HRCT (in ml and % of total lung volume), representative of interstitial lung abnormalities (ILA) will be computed, comparing PRM151 *vs.* placebo (separately) in patients with SVC breathhold at CT scanning ≥90% of SVC supine, with a similar approach to the one used

for the primary analysis (statistical tables 14.2.19.1.1.1 to 14.2.19.2.3.2, Figure 14.2.16.1.1 to 14.2.16.2.2).

For all categories of lung features (including PVV), the change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) wil be computed in subjects treated with PRM-151 and placebo, depending on the completeness and usability of the obtained data.

Change in Patient Reported Outcomes will be assessed based on the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and Leicester Cough Questionnaire (LCQ). Descriptive statistics for raw values and change from Baseline to each visit in total score of both questionnaire will be computed by treatment group. Differences between treatment groups in change from baseline to week 28 for total score of each questionnaire will be tested using a similar approach to the one used for the primary ananlysis (see section 5.2.5.1). These analysis will be performed on both the ATS and the PP data sets (Statistical tables 14.2.20.1.1 to 14.2.20.3.2 and 14.2.21.1.1 to 14.2.21.3.2, Figures 14.2.17.1 to 14.2.17.2 and 14.2.18.1 to 14.2.18.2). All results of K-BILD and LCQ will be reported in Listings 16.2.6.4.1 to 14.2.6.4.2.2 and 16.2.6.5.1 to 16.2.6.5.2.2.

For the LCQ, in addition to the above approach, frequency of patients with changes below or above 1.3 (identified as the minimal important difference) will be tabulated by treatment groups at week 4, 8, 12, 16, 20, 24 and 28 (Statistical table 14.2.21.4.1 and 14.2.21.4.2).

Descriptive statistics for raw values at each visit and change from baseline to each visit in anti-Pentraxin-2 antibodies measurements will be computed by treatment group. This analysis will be performed on both the ATS and the PP dataset (Statistical 14.2.22.1.1 to 14.2.22.2.2). Individual measurements of anti-pentraxin-2 antibodies will be reported in Listing 16.2.6.8.

***EO3:*** *To assess the use of quantitative imaging in IPF*

The correlation between baseline FVC [% predicted], DLCO (corrected for Hb, [% predicted]), TLC by nitrogen washout, PROs and 6MWD and total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of ILA by quantitative imaging, as well as change from Baseline to Week 28 in FVC [% predicted], DLCO (corrected for Hb, [% predicted]), TLC by nitrogen washout, PROs and 6MWD and change from Baseline to Week 28 in total lung volume and volume of parenchymal features on HRCT (in ml and % of total lung volume) representative of ILA will be computed. This analysis will be performed on both the ATS and the PP dataset (Statistical tables 14.2.23.1.1 yo 14.2.23.1.2).

For all categories of lung features (including PVV) the correlation between (i) change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) and (ii) change from baseline to week 28 in FVC [% predicted] will be computed. This analysis will be performed on both the ATS and the PP dataset (Statistical tables 14.2.23.2.1 yo 14.2.23.2.2).

For all categories of lung features (including PVV) the correlation between (i) change from baseline to week 28 in volume of a given lung feature (both in ml as well as in % of total lung volume) and (ii) change from baseline to week 28 in DLCO will be computed. This analysis will be performed on both the ATS and the PP datasets (Statistical table 14.2.23.3.1 yo 14.2.23.3.2).

The impact of inspiratory effort on results of HRCT quantitative imaging will be assessed by (Statistical table 14.2.23.4.1 to 14.2.23.4.2, Figure 14.2.19.1 to 14.2.19.2):
1. Calculating the proportion of patients performing spirometry guided HRCT with a SVC breathhold at CT scanning ≥90% of SVC supine at baseline and at week 28
2.The correlation of SVC breathhold at CT scanning and SVC supine at baseline and at week 28
3.The correlation between (i) baseline Total lung volume by quantitative imaging and (ii) baseline TLC by nitrogen washout, seperately for patients with SVC breathhold at CT scanning ≥90% of SVC supine, and for patients with SVC <90% or not receiving spirometry-guided HRCT.

***EO4:*** *To assess the impact of PRM-151, disease pathogenesis and disease progression on exploratory serum, cellular and genetic biomarkers*

To assess the impact of PRM-151 on exploratory biomarkers, descriptive statistics for change from baseline to week 28 in biomarkers will be computed by treatment group and by baseline genetic status (MUC5B and TLR polymorphism separately). These analysis will be performed on both the ATS and the PP dataset (Statistical table 14.2.24.1 and 14.2.24.2). Individual biomarker values will be reported in Listing 16.2.6.6. All or part of these analyses may be provided at a later stage than the rest of the analyses described in the SAP, might the corresponding data not be available at the time of the database lock. It is currently anticipated that baseline genetic status will be avialable, but biomarkers will not.

***Additional exploratory analysis: ADA vs. FVC [% predicted]***
The relationship between Anti-Pentraxin 2 antibodies (ADA) presence and level of FVC [% predicted] in time will be studied by modelling the influence of presence/absence (and/or level) of ADA in the repeated measures mixed model used for the primary efficacy analysis (see section 5.2.5.1) and if relevant using non-parametric spline functions. The most parcimonious model will be chosen on the basis of the AIC (Statistical table 14.2.25.1 and 14.2.25.2).

***Additional exploratory analysis: Baseline characteristics vs. FVC***
If data lend themselves to it, additional exploratory analysis will be done to test for interaction between baseline characteristics (e.g., FVC/DLCO/6MWD) and change in FVC.

***Exploratory analysis of PK/PD relationship***

Descriptive statistics and correlation will be computed to explore the relationship of Pentraxin-2 levels vs FVC [% predicted]/FVC [ml]/slope of FVC ml at week 24 and 28, and the relationship of

Pentraxin-2 vs other PFTs/PROs/6MWT (Statistical table 14.2.26.1 and 14.2.26.2). If relevant the corresponding scatter plot will be produced.

***Exploratory analysis of relationship between Pentraxin-2 levels and ADA***
Correlation coefficient between Pentraxin-2 levels and ADA titer at week 28 will be computed (Statistical tables 14.2.27.1 and 14.2.27.2) and a scatterplot prepared (using logarithmic coordinates for titers).

***Exploratory analysis of acute exacerbations***
Tabulation of each type of acute exacerbations will be produced (Statistical table 14.2.28.1.1 and 14.2.28.1.2). Descriptive statistic and Kaplan-meier curve will be computed by treatment group for time to first reported acute exacerbation (Statistical tables 14.2.28.2.1 and 14.2.28.2.2).

***Additional exploratory analysis: FVC [% predicted] separately on pirfenidone and nintedanib***
The same model as the one for the primary analysis (see section 5.2.5.1) will be used separately on (i) patient on a stable dose pirfenidone and (ii) patient on a stable dose of nintedanib (Statistical table 14.2.20.1.1 to 14.2.20.2.2).

***Additional exploratory analysis: time variation in historic FVC [% predicted; ml] measurements:***
The time variations in historic FVC [% predicted] data (see section 8) will be modelled using a linear mixed effect model with random intercept and slope, with available historic FVC measurements for each patient (until baseline, baseline included) as dependent variable (outcome) and time (continuous variable calculated as the actual number of days before baseline) as explanatory variables (Statistical table 14.2.30.1.1 to 14.2.30.1.2, Figure 14.2.21.1.1 to 14.2.21.1.2). This analysis will be repeated using historic FVC [ml] measurement as dependent variable. (Statistical table 14.2.30.2.1 to 14.2.30.2.2, Figure 14.2.21.2.1 to 14.2.21.2.2). All available individual measurements will be provided in Listing 16.2.6.13.

### *5.2.6 Safety analyses*

Safety analysis will be based on the incidence, intensity, and type of adverse events, incidence of respiratory decline, Infusion related reactions, and clinically significant changes in the subject's physical examination, vital signs and clinical laboratory results. Safety variables will be tabulated and presented for all subjects who have received any amount of study medication.

#### 5.2.6.1 Adverse events

*Adverse event listings:*

AE listings will be presented and sorted by treatment group, subject, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study and will include durat ion of each episode.

The following listings will be produced:

- Listing of Adverse Events (Listing 16.2.7.1): All adverse events for each patient, including the same event on several occasions, giving both preferred term and the original term used by the investigator. The listing will be sorted by site and by treatment group and should include: Patient identifier / Age, race-ethnicity, sex, weight, height / The adverse event (preferred term, reported term) / Duration of the adverse event / Severity (mild, moderate, severe) / Seriousness (serious, non-serious) / Action taken with study drug (dose reduced, treatment interrupted-delayed, treatment permanently discontinued-omitted, none, not applicable) / Outcome (resolved, resolved with sequelae, ongoing, unknown) / Relationship to study drug (not related, possibly related, probably related) / Date of onset or date of clinic visit at which the event was discovered / Timing of onset of the adverse event.

- Listing of Deaths (Listing 16.2.7.2) and Serious Adverse Events containing the same information as above.

*Adverse events tabulations:*

Tabulation of adverse events will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events (if relevant). The following tables will be produced for the whole SAF population as well as by treatment group:

Summary of AE (Statistical Table 14.3.3):

- Any AE
- Any TEAE
- Any TEAE leading to permanent study treatment discontinuation
- Any TEAE leading to study discontinuation
- Any TEAE of severe intensity
- Any possibly or probably related TEAE
- Any SAE
- Any TESAE
- Any TESAE leading to study treatment permanent discontinuation
- Any TESAE leading to study discontinuation (optional)
- Any TESAE considered related to the study treatment
- Deaths (if any)
-

Detailed Tables on TEAEs:

- All TEAE by SOC and PT (Statistical Table 14.3.4.1)
- Most frequent TEAEs by SOC and PT and decreasing frequency (Statistical Table 14.3.4.2)
- All possibly or probably related TEAEs by SOC and PT (Statistical Table 14.3.4.3)
- All TEAE by SOC, PT and intensity (Statistical Table 14.3.4.4)

- All TEAE leading to permanent study drug discontinuation by SOC and PT (Statistical Table 14.3.4.5, only produced if more than 5 events)
- All TEAE leading to permanent study discontinuation by SOC and PT (Statistical Table 14.3.4.6, only produced if more than 5 events)

Detailed Tables on TESAEs:

- Any TESAE by SOC and PT (Statistical Table 14.3.5.1)
- All possibly or probably related TESAEs by SOC and PT (Statistical Table 14.3.5.2, only produced if more than 5 events)
- All TESAE by SOC, PT and intensity (Statistical Table 14.3.5.3)
- All TESAE leading to permanent study drug discontinuation by SOC and PT (Statistical Table 14.3.5.4, only produced if more than 5 events)
- All TESAE leading to permanent study discontinuation by SOC and PT (Statistical Table 14.3.5.5, only produced if more than 5 events)
- Death: all causes of mortality and mortality due to respiratory declines (Statistical Table 14.3.5.6)

#### 5.2.6.2 Respiratory decline events

Tabulation of respiratory decline events will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events. The following tables will be produced for the whole SAF population as well as by treatment group:

- All respiratory decline events by PT (Statistical tables 14.3.6.1)
- All respiratory decline events by PT and intensity (Statistical tables 14.3.6.2)
- All respiratory decline events by PT and seriousness (Statistical tables 14.3.6.3)

#### 5.2.6.3 Infusion related reactions

Tabulation of infusion related reactions will present for each cell the following information: number of patients with at least one occurrence of the event, corresponding percentage and number of events. The following tables will be produced for the whole SAF population as well as by treatment group:

- All infusion related reactions by PT (Statistical tables 14.3.7.1.1)
- All infusion related reactions by PT and intensity (Statistical tables 14.3.7.1.2)
- All infusion related reactions by PT and seriousness (Statistical tables 14.3.7.1.3)

The potential influence of Anti-Pentraxin 2 antibodies (ADA) and occurrence of IRR will be studied by producing the same tables as described above breaking down the patients according to presence/absence of ADA (Statistical tables 14.3.7.2.1, 14.3.7.2.2 and 14.3.7.2.3).

#### 5.2.6.4 Laboratory safety variables

*Table of laboratory safety variables:*

Laboratory evaluations will be summarized by visit and by treatment group on the SAF population. For each hematology, chemistry and coagulation variables we will compute:

- Quantitative descriptive statistics on both raw values and change from baseline (Statistical tables 14.3.8.1-2, 14.3.9.1-2 and 14.3.10.1-2)
- Qualitative descriptive statistics (individual patient changes):
    - Number of patients with values: normal, abnormal NCS, abnormal CS (Statistical table 14.3.8.2, 14.3.9.2 and 14.3.10.3)
    - Shift Tables from baseline to each visit (Statistical table 14.3.8.3, 14.3.9.3 and 14.3.10.3)

Depending of their number the clinically significant laboratory abnormalities will not be tabulated but rather presented in individual data listings (Listings 16.2.8.1 to 16.2.8.4).

*Figures on laboratory safety variables:*

All individual values of a given laboratory measurement for each patient will be produced. When available, the LLN and ULN will be displayed on the graph. Figures will be produced for all hematologic, chemistry and coagulation variables (Figures 14.3.2).

To facilitate the exploration of potential Drug-Induced Liver Injury (DILI), eDISH (Evaluation of Drug-Induced Serious Hepatotoxicity) plots, plotting peak total bilirubin level versus peak ALT level, both expressed as multiples of the upper limit of normal on a base 10 logarithmic scale, together with mlines identifying the normal range and 2 times the upper lipit of the normal range for total bilirubin and three times the upper limit of the normal range for ALT, will be presented (Figure 14.3.3).

*Listing of laboratory safety variables:*

Listings of all safety-related laboratory test including pregnancy test (Listings 16.2.8.1 to 16.2.8.4) will be prepared, presenting patient id, identification of time point, age, sex, race-ethnicity, weight, identification of laboratory test, raw result, evaluation (normal, abnormal…), investigator judgment on clinical significance on abnormal values. This listing will be presented by treatment group.

#### 5.2.6.5 Physical exams

For all the variables collected during physical examinations at baseline, the frequencies of normal, abnormal NCS and abnormal CS values will be reported by treatment group (Statistical table

14.3.11). All individual measurements collected at baseline and during the subsequent visits will be provided in Listing 16.2.9.1.

#### 5.2.6.6 Vital signs

- Quantitative descriptive statistics: mean, median, standard deviation, min, max based on raw values and change from baseline (Statistical tables 14.3.12.1 and 14.3.12.2)
- Qualitative descriptive statistics (individual patient changes):
    - Proportion of patients with abnormal values (Statistical table 14.3.12.3)
    - Shift Tables presenting the number of patients with normal/abnormal values at baseline and then at each cycle (Statistical table 14.3.12.4)

All individual measurements will be provided in Listing 16.2.9.2.

#### 5.2.6.7 Concomitant medication

Two tables with the proportions of subjects in the SAF population taking each concomitant medication will be provided for:

- Concomitant medications at baseline (started before baseline and stopped after baseline or still ongoing at end of treatment) by treatment group (Statistical table 14.3.13.1).
- Concomitant medications started after baseline by treatment group (Statistical table 14.3.13.2).

Tables summarizing the use of pirfenidone and nintedanib (proportion of patients using each drug) at baseline and started after baseline by treatment group will be prepared on the SAF population (Statistical table 14.3.13.3, 14.3.13.4).

## 5.3 Statistical/Analytical issues

### *5.3.1 Adjustments for Covariates*

All comparisons of change from baseline to a given visit between treatment groups performed using ANOVA models and pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF, are adjusted for stratification levels.

Analysis of time variation in a given variable using Linear Mixed Models and pooling subjects on a stable dose of pirfenidone or nintedanib with subjects not on other treatment for IPF, are all adjusted for baseline measurements of the response variable and stratification levels.

### *5.3.2 Handling of Dropouts or Missing Data*

*Missing data in efficacy analysis:*

The statistical model (linear mixed models for repeated measures) used for the primary and most secondary efficacy analyses will be used without imputation of missing values and are valid under the assumption of missingness at random.

Multiple imputation techniques will be used for the sensitivity analysis on the initially planned primary analysis (see Section 5.2.5.1).

All available efficacy and safety data will be included in data listings and tabulations.

*Missing or incomplete dates:*

For all listings, missing or incomplete dates will be left as they were recorded.

For calculation / sorting / assignation based on dates (*e.g.*, treatment emergent AEs, concomitant medications…), the following rules will apply:

- The most conservative approach will be considered (*i.e.*, if the onset date of an AE/concomitant medication is missing / incomplete, it will be assumed to have occurred during the study treatment phase (*i.e.*, a TEAE for AEs) except when the partial onset date or other available data indicates differently (*e.g.*, start date day missing, but month before the month of baseline date, or stop date before baseline date).
- Medical history or disease diagnosis with missing/incomplete date will be assumed to have occurred before any study treatment except when the partial onset date or other available data indicates differently.
- Assignations based on dates will be reviewed and confirmed or infirmed during the data review meeting
- Missing or partial start or end dates of IMP administration, if any, will be reviewed during the data review meeting.

### *5.3.3 Interim Analyses and Data Monitoring*

No formal interim data analysis is planned for the study.

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

The committee is planned to review the safety data in an unblinded manner, and the efficacy data will be provided semi-blinded by group. However, DMC may request study drug treatment code for group in order to complete their assessment of safety/benefit risk. This request will only be made to the unblinded statistician, as stated in the DMC Charter.

### 5.3.4 Multicentre studies

This study is planned to be conducted in 18 study sites in 8 countries. Because of the too small expected numbers of patients within sites, all the analysis will be performed on the pooled data over countries and study sites.

### 5.3.5 Multiple Comparison/Multiplicity

There will be one single primary efficacy analysis, from which the conclusions on efficacy will be drawn. Consequently, there is no issue of multiplicity of primary analyses and no need to adjust the significance level.

### 5.3.6 Use of an "Efficacy Subset" of Patients

Two efficacy analyses populations are defined, the ATS and the PP. The definition of these populations is available in Section 3. The primary efficacy analysis will be conducted on the ATS. No patient with available post-treatment efficacy data are excluded from the ATS and, consequently from the primary efficacy analysis.

The PP population will be used to conduct a sensitivity analysis and assess the robustness of the primary efficacy analysis conclusions. Any substantial difference between the two analyses will be explored and discussed.
In addition, the SAP planned to conduct the primary analysis on the Full analysis Set. This was then changed to the ATS. Nevertheless, the initially planned analysis on the FAS will be conducted and provided as an additional sensitivity analysis to further assess the robustness of the primary efficacy analysis conclusions and in particular to assess the impact of excluding patient without any post-baseline efficacy measurement from the FASATS population. Any substantial difference with the result obtained for the primary efficacy analysis on the ATS will be explored and discussed.

### 5.3.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

### 5.3.8 Examination of Subgroups

Sensitivity analysis of the primary endpoint and some secondary efficacy analyses aim at exploring difference in response variables between the levels of stratification. See sections 5.2.5.1 and 5.2.5.2 for details.

## 5.4 Data handling conventions

### *5.4.1 Baseline definitions*

For both the efficacy and safety endpoints the last observation prior to the first dose of study treatment administration will be used as the baseline value. This will usually correspond to the measurement performed at day1 week 0 before first-dose. However, in case of missing value at day 1 week 0 the last available value recorded during screening will be used as baseline value.

### *5.4.2 Retest, Outliers*

#### 5.4.2.1 Retests

The retests will be managed as follow:

- Any retest before baseline : the last available value recorded before baseline (day1 week 0) will be used as the baseline
- Any other retest: data will be reviewed and decision will be made during the blind review on the basis of the following rules:
    - Retest on efficacy data: non-missing value the closest to the scheduled visit will be used
    - Retest on safety data: the worst recorded value will be used

#### 5.4.2.2 Outliers

All outlier data will be reviewed during the data review meeting and decisions regarding their use in the statistical analyses will be made.

### *5.4.3 Unscheduled visits*

All unscheduled visit data will be presented in the individual data listings and used in all safety analyses. For categorical results: reallocation to the visit following last infusion. In case of several data the worst observation will be used in tabulation. For numeric results the first value among worst abnormality/grade will be used. These reallocation will be reviewed in blind review meeting.

### *5.4.4 Visit windowing*

The agreement between realized visit date and the expected visit time frame will be reviewed during blind review meeting.

For premature discontinuated patient, all data collected during the End of Study visit will be reallocated to the visit following last infusion.

# 6 Modifications from the statistical sections in the protocol

## **6.1** Change in the primary efficacy analysis

According to the protocol, the primary efficacy analysis was to be the Full Analysis Set (FAS), defined as all randomized patients having received at least one administration of the study medication with a baseline and at least one post-baseline assessment of FVC [% predicted] (primary efficacy criterion) available.
Limiting the population to subjects having at least one post-baseline assessment of FVC [% predicted] draws the efficacy population further from the intention to treat paradigm than the exclusion of only untreated patients. Consequently, it has been decided to change the primary efficacy analysis population to the All Treated Set (ATS, see section 3.2) defined as all randomized subjects who have received at least one administration of the investigational medicinal product (IMP).

In addition to this change of population, it has been decided to change the analysis model from the initially planned ANOVA model on change from baseline to week 28 to a linear mixed effect model with random intercept using all measurements available until Week 28 used to compute the estimate of the between group difference in change from baseline at week 28.

## **6.2** Changes in secondary efficacy analyses

All secondary efficacy analyses will be performed on both the ATS and the PP.

To be consistent with the primary efficacy analysis, the same analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in normal lung parenchyma (normal + mild LAA) and interstitial lung abnormalities (ILA) as quantified on high-resolution CT (HRCT) imaging analysis (SO1).

To be consistent with the primary efficacy ananlysis, the same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in mean FVC% predicted, separately in subjects on a stable dose of pirfenidone or nintedanib and in subjects not on other treatments for IPF (SO2).

To be consistent with the primary efficacy ananlysis, the same analysis model as those of the primary analysis (see section 5.2.5.1) will be used, instead of the ANOVA model initially planned, to determine the effect size of PRM-151 relative to placebo in change from Baseline to Week 28 in

normal lung (defined as normal + mild LAA) parenchyma and interstitial lung abnormalities (ILA) as quantified on HRCT imaging analysis (SO3).

Odds ratios wil be computed in addition to quantitative statistics to determine (SO6) the effect size of PRM-151 relative to placebo on pulmonary function and mean change in FVC% predicted.

To be consistent with the primary efficacy ananlysis, the same descriptive statistics and analysis model as those of the primary analysis (see section 5.2.5.1) will be used to determine the effect size of PRM-151 relative to placebo on 6MWD (SO7) and DLCO (SO8).

**6.3** Changes in exploratory efficacy analyses

All exploratory efficacy analysis will be performed on both the ATS and the PP.

It was initially planned (EO1) to evaluate the efficacy and estimate the size of effect of PRM-151 relative to placebo in change from baseline to weeks 4, 8, 12, 16, 20, and 24 in FVC % predicted, FVC in ml and 6 minute walking distance using mixed models with random intercepts. To obtain a better decription of individual variability, both random intercepts and random slopes will be used.

The following not initialy planned exploratory analysis were added (see section 5.2.5.3 for details):

- To assess the use of quantitative imaging in IPF (E03)
- To explore the relationship between Anti-Pentraxin 2 antibodies (ADA) presence and level of FVC [% predicted] in time
- To explore PK/PD relationship.
- To explore relationship between Pentraxin-2 levels and ADA
- To explore acute exacerbations
- To explore time variations in FVC % predicted separately in patient (i) on stable dose of pirfenidone and (ii) on a stable dose of pirfenidone.

# 7 Software documentation

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

# 8 Derived data

| Derived variable | Derivation algorithm |
|---|---|
| Change from baseline to visit V (continuous) | Change from baseline of variable $X=X_{(Visit\ V)}-X_{(Baseline)}$<br>o Negative values indicate a decrease in X<br>o Positive values indicate an increase in X |

| | |
|---|---|
| Percent change from baseline to visit V (continuous) | Percent change from baseline of variable X=100 *[$X_{(Visit\ V)}$-$X_{(Baseline)}$]/ $X_{(Baseline)}$<br>o Negative values indicate a decrease in X<br>o Positive values indicate an increase in X |
| Treatment compliance | Continuous variable: The compliance $C_i$ for patient *i* will be computed according to:<br>$$C_i = \frac{D_i^t * 100}{D_i^p}$$<br>where $D_i^p$ mg is the total amount (mg) of IP prescribed to patient *i* and $D_i^t$ is the total amount (mg) of IP actually taken by the patient during the study i.e., before the end of study for patient *i*. |
| Treatment compliance (categorical) | Categorial variable with three modalities:<br>• $C_i < 80\%$<br>• $80\% \leq C_i < 120\%$<br>• $C_i \geq 120\%$ |
| Vital Sign abnormalities | • Heart rate: <50 or >90<br>• Respiratory rate: <12 or >20<br>• Body temperature: <36.5°C or >37.5°C<br>• Diastolic Blood Pressure: <60 or >90<br>• Systolic Blood Pressure: <90 or >140<br>• Oxygen Saturation: <90 |
| Event Duration | (End Date) – (Start Date) + 1 |
| Total Lung Volume in ml (TLV) | Total lung volume (excluding vessel volume) in ml |
| Normal Lung Volume in ml (NLV) | NLV=Areas of Normal lung in ml + Mild Low Attenuation Area (LAA) in ml |
| % of Normal Lung Volume | 100 * (NLV in ml) / (TLV in ml) |
| % of mild Low Attenuation Areas (LAA) | 100 * (mild LAA in ml) / (TLV in ml) |
| % of moderate Low Attenuation Areas (LAA) | 100 * (moderate LAA in ml) / (TLV in ml) |
| % of severe Low Attenuation Areas (LAA) | 100 * (severe LAA in ml) / (TLV in ml) |
| % Ground Glass (GG) | 100 * (GG in ml) / (TLV in ml) |

| | |
|---|---|
| % Honeycombing (HC) | 100 * (HC in ml) / (TLV in ml) |
| % Reticular Changes (RC) | 100 * (RC in ml) / (TLV in ml) |
| Interstitial Lung Abnormalities (ILA) in ml | (ILA in ml) = (GG in ml) + ( RC in ml) + (HC I ml) |
| % Interstitial Lung Abnormalities (ILA) | %ILA = %GG + %RC + %HC |
| Historic FVC (% predicted) | (Historic FVC % predicted) = [Historic FVC (mL)/ Reference Result of FVC (mL) at baseline)]*100 |

# 9 Tables, Figures and Listings

## 9.1 List of tables

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| | |
|---|---|
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| 14.2.9.1.a to 14.2.9.2.a | (SO6) Secondary analyses: Effect size in PRM-151 - Treatment Effect |
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| 14.2.10.1.1 to 14.2.10.1.2 | (SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - raw values at each visit |
| 14.2.10.2.1 to 14.2.10.2.2 | (SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - change from baseline to each visit |
| 14.2.10.3.1a to 14.2.10.3.2a | (SO7) Secondary Efficacy Analysis: 6 Minute Walk Distance - Anova table |
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| 14.2.13.1.c to 14.2.13.2.c | (EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis- Least Square Means by stratum at each visit |
| 14.2.13.1.d to 14.2.13.2.d | (EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis- Least Square Means for change from baseline at each visit |
| 14.2.14.1.1.a to 14.2.14.1.2.a | (EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Anova table - No Background Therapy |
| 14.2.14.1.1.b to 14.2.14.1.2.b | (EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Model parameter estimates - No Background Therapy |
| 14.2.14.1.1.c to 14.2.14.1.2.c | (EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Least Square Means at each visit - No Background Therapy |
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| 14.2.14.2.1.a to 14.2.14.2.2.a | (EO1) Exploratory analyses: FV [%predicted] - Random Slope Analysis Separately for each stratum - Anova table - Pirfenidone or Nintedanib |
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| 14.2.16.1.1.1 to 14.2.16.1.1.2 | (EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Raw values at each visit - No Background Therapy |
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| 14.2.16.1.3.1.c to 14.2.16.1.3.2.c | (EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Least Square Means at each visit - No Background Therapy |
| 14.2.16.1.3.1.d to 14.2.16.1.3.2.d | (EO1) Exploratory analyses: FV [ml] - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - No Background Therapy |

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| 14.2.17.1.c to 14.2.17.2.c | (EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis- Least Square Means by stratum at each visit |
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| 14.2.18.1.3.1.d to 14.2.18.1.3.2.d | (EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - No Background Therapy |
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| 14.2.18.2.3.1.d to 14.2.18.2.3.2.d | (EO1) Exploratory analyses:6-Minute Walk distance - Random Slope Analysis Separately for each stratum - Least Square Means for change from baseline at each visit - Pirfenidone or Nintedanib |
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