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

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PRM-151 IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS**

STUDY NUMBER:	WA42293 (also known as PRM-151-303)
STUDY NAME:	STARSCAPE
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STATISTICAL ANALYSIS PLAN APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2, 26 October 2020.

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1	See electronic signature on the last page of this document	Version 5, 28 April 2022

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description
6MWD	6-minute walk distance
6MWT	6-minute walk test
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
ALAT	Latin American Thoracic Society
ATS	American Thoracic Society
BMI	body mass index
CI	Confidence Interval
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DL_{CO}	carbon monoxide diffusing capacity
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
EuroQol	European Quality of Life Scale
ERS	European Respiratory Society
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
Hgb	hemoglobin
HR	hazard ratio
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IPF	idiopathic pulmonary fibrosis
ITT	intent to treat
IV	intravenous
IxRS	interactive voice/web-based response system
JRS	Japanese Respiratory Society
LLoQ	lower limit of quantification
MAR	missing at random
MDD	minimally detectable difference

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NCI	National Cancer Institute
NMPA	National Medical Products Administration
OLE	open-label extension
PD	pharmacodynamic
PFT	pulmonary function test
PK	pharmacokinetic
PRO	patient-reported outcomes
Q4W	every 4 weeks
zinpentraxin alfa	recombinant human pentraxin 2; PRM-151
SAE	serious adverse events
SAP	Statistical Analysis Plan
SGRQ	St. George Respiratory Questionnaire
SOC	standard of care
SMQs	standardized MedDRA queries
UCSD-SOBQ	University of California, San Diego-Shortness of Breath Questionnaire
UIP	usual interstitial pneumonia
VAS	visual analog scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details on the study design, outcome measures, and statistical analysis plan for Study WA42293. The analyses and endpoints specified in this document supersede the analysis plan described in the study protocol. The International Nonproprietary Name (INN) zinpentraxin alfa is now the preferred name of the study drug under investigation (rather than PRM-151 or rhPTX-2); it will be used throughout this SAP.

1.1 OBJECTIVES, ENDPOINTS AND ESTIMANDS

This study will evaluate the efficacy, safety, and pharmacokinetics of zinpentraxin alfa compared with placebo in participants with idiopathic pulmonary fibrosis (IPF). Specific objectives and corresponding endpoints for the study are outlined in Table 1. The Clinical Adjudication Committee mentioned in the table below and the rest of the SAP (with the exception of the Anaphylaxis Adjudication Committee introduced in Section 1.2.2.5) refers to the Clinical Adjudication Committee reviewing acute or suspected exacerbation of IPF, hospitalization due to respiratory causes, and death.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of zinpentraxin alfa plus SOC treatment as needed compared with placebo plus SOC treatment as needed	• Absolute change from baseline at Week 52 in FVC (mL)
Key Secondary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of zinpentraxin alfa plus SOC treatment as needed compared with placebo plus SOC treatment as needed	• Absolute change from baseline at Week 52 in 6MWD (in meters)
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of zinpentraxin alfa plus SOC treatment as needed compared with placebo plus SOC treatment as needed	• Absolute change from baseline at Week 52 in FVC% predicted • Time to disease progression, defined as time to first occurrence of ≥10% absolute decline in FVC% predicted, ≥15% relative decline in 6MWD, or death • Time to first respiratory-related hospitalization (defined as non-elective hospitalization due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF, as determined by the Clinical Adjudication Committee) • Absolute change from baseline at Week 52 in UCSD-SOBQ score

	• Absolute change from baseline at Week 52 in SGRQ Total Score • Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF, as determined by the Clinical Adjudication Committee • Absolute change from baseline at Week 52 in Hgb-corrected carbon monoxide diffusing capacity (DL_{CO}) % predicted • Survival, as measured by all-cause mortality
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of zinpentraxin alfa plus SOC treatment as needed compared with placebo plus SOC treatment as needed	• Absolute change from baseline at Week 52 in FVC% predicted and FVC (mL), by baseline concomitant medication stratum • Absolute change from baseline at Week 52 in FVC% predicted and FVC (mL), by mucin 5B (MUC5B) risk allele positive or negative status • Absolute change from baseline at Week 52 in 6MWD (m), by baseline concomitant medication stratum • Proportion of patients who progress on the UCSD-SOBQ, as indicated by an increase in score of 10 points or greater • Proportion of patients who progress on the SGRQ total score, as indicated by an increase in score of 7 or greater • Change from baseline to Week 52 in SGRQ Individual Domains (Symptoms, Activity, and Impacts) Score • Proportion of patients who progress on the SGRQ Symptoms Domain, as indicated by an increase in score of 8 or greater • Proportion of patients who progress on the SGRQ Activity Domain, as indicated by an increase in score of 5 or greater • Proportion of patients who progress on the SGRQ Impacts Domain, as indicated by an increase in score of 7 or greater • Absolute change from baseline at Week 52 in quantitative imaging analysis parameters of HRCT scan of the thorax • Length of hospital stay for respiratory-related hospitalizations • Total time in intensive care units due to respiratory causes • Unscheduled outpatient clinic/urgent care/emergency room utilization related to respiratory events

	• Number of acute exacerbations during the 52 weeks; as determined by the Clinical Adjudication Committee • Survival as measured by IPF-related mortality • Survival as measured by respiratory-related mortality • Disease progression and subsequent start of oxygen supplementation • Change in PFT parameters (FVC, DL_{CO}) or 6MWD from baseline at Week 52 between SARS-CoV2 antibody positive compared with negative patients (present at baseline) • Change in PFT parameters (FVC, DL_{CO}) or 6MWD from baseline at Week 52 in patients who develop SARS-CoV2 antibodies during treatment (not present at baseline) • Absolute change from baseline at Week 52 in FVC (mL) by selected countries
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of zinpentraxin alfa plus SOC treatment as needed compared with placebo plus SOC treatment as needed	• Incidence and severity of adverse events, with severity determined according to the 5-point severity scale (NCI CTCAE v.5.0) • Incidence and severity of IRRs and other adverse events of special interest • Proportion of patients permanently discontinuing study treatment due to adverse events • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of zinpentraxin alfa	• Plasma concentrations of zinpentraxin alfa at specified timepoints
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure and the efficacy and safety of zinpentraxin alfa	• Relationship between PK for zinpentraxin alfa and efficacy endpoints • Relationship between PK for zinpentraxin alfa and safety endpoints

Immunogenicity Objective	Corresponding Endpoints
• To evaluate the immune response to zinpentraxin alfa	• Prevalence of ADAs at baseline • Incidence of ADAs during the study
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify and/or evaluate biomarkers that are predictive of response to zinpentraxin alfa (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to zinpentraxin alfa, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of zinpentraxin alfa activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
Exploratory Health Status Utility Objective	**Corresponding Endpoint**
• To evaluate health status utility scores of participants treated with zinpentraxin alfa plus SOC treatment as needed compared with placebo plus SOC treatment as needed	• Absolute change from baseline in EuroQol EQ-5D-5L index-based, and VAS scores at Week 52

6MWD = 6-minute walk distance; 6MWT= 6-minute walk test; ADA=anti-drug antibody; CTCAE= Common Terminology Criteria for Adverse Events; DL_{CO} = carbon monoxide diffusing capacity; EQ-5D-5L =EuroQol 5-Dimension, 5-Level Questionnaire; FVC = forced vital capacity; Hgb=hemoglobin; HRCT = high-resolution computed tomography; HRQol=health-related quality of life; NCI=National Cancer Institute; PD=pharmacodynamic; PFT = pulmonary function test; PK=pharmacokinetic; SGRQ = St. George Respiratory Questionnaire; SOC = standard of care; UCSD-SOBQ = University of California, San Diego-Shortness of Breath Questionnaire; VAS=visual analogue scale.

Primary Estimand

The primary efficacy objective is to evaluate the effect of zinpentraxin alfa plus standard of care (SOC) treatment as needed compared with the matching placebo plus SOC treatment as needed on disease progression at Week 52, regardless of changes to the initial treatment regimen (including randomized drug and any associated treatment) and in the absence of lung transplantation. The primary estimand is the difference in mean absolute change from baseline at Week 52 in forced vital capacity (FVC) mL between zinpentraxin alfa and placebo treated patients. The primary estimand is further described by the following attributes:

- Population: adults diagnosed with IPF who meet the inclusion/exclusion criteria presented in Section 4.1 of the protocol.
- Treatment: study drug (zinpentraxin alfa or placebo) as randomized, in combination with any background or additional treatment (i.e., zinpentraxin alfa or placebo taken alone or as an add-on to SOC with pirfenidone or nintedanib, dosed as required) including all changes in SOC treatment and all other additional treatments, with the exclusion of lung-transplantation.
- Variable: absolute change from baseline at Week 52 in FVC mL.
- Population-level summary measure: between randomized treatment difference in mean change from baseline at Week 52 in FVC mL.
- Intercurrent events:
  - Change to initial treatment regimen: The treatment effect of interest is irrespective of changes to the initial treatment regimen, which include changes to study drug (including treatment discontinuation), changes to standard of care, and the use of prohibited medication. Therefore, all data collected after changes to the initial treatment regimen will be included in the analysis. Any data missing after changes to the initial treatment regimen will be assumed to be missing at random (MAR). A sensitivity analysis described in Section 4.3.3.1 will assess the impact of assuming that data missing after treatment discontinuation is MAR.
  - Death: Deaths are expected to be rare as the study plans to include patients with a life expectancy longer than the study duration. Given that deaths are expected to be rare, and the observation that conservative imputation of missing, post-death data for continuous FVC (mL) outcomes introduces highly influential outliers, deaths will be treated with a hypothetical strategy. A sensitivity analysis described in Section 4.3.3.1.1 will assess the impact of this strategy on treatment effect estimation and inference.
  - Lung transplantation: Lung transplantation is expected to be rare during the study, as patients likely to receive a lung transplantation during the study are excluded. Furthermore, the treatment effect of interest is in the hypothetical scenario that lung transplantations are unavailable, since assessments following lung transplantation are no longer reflective of diseased lung(s).

In some instances, FVC can improve to over 80% following lung transplantation, or even 100% for bilateral lung transplantation 6-12 months after surgery (Hernandez et al. 2018). Therefore, any data recorded after lung transplantation will be excluded from the analysis and treated as missing data because such data is not compatible with this hypothetical strategy.

- Hospitalization for COVID-19: The treatment effect of interest is irrespective of COVID-19 hospitalization, given that COVID-19 hospitalizations will likely continue for the population of interest for the foreseeable future. Therefore, all data recorded after COVID-19 hospitalization will be included in the analysis. Any missing data after COVID-19 hospitalizations will be assumed to be MAR.

In general, with the exception of data collected after lung transplantation, all observed outcome data will be included in the analysis. All missing data, including data excluded after lung transplantations and missing data due to death, will be considered similar to data from other patients in the same treatment group with the same baseline characteristics with no such missing data (compatible with MAR assumption). Sensitivity analyses addressing missing data assumptions are described in Section 4.3.3.

Table 2 below summarizes the handling of intercurrent events for the primary estimand.

Table 2 Primary Estimand Analysis Strategy for Intercurrent Events

Intercurrent Event (ICE)		Analysis strategy
Any change to randomized treatment	Temporary study drug discontinuation	Treatment policy
	Permanent study drug discontinuation	All measurements post ICE analyzed
	Temporary or permanent change in study drug dose	
	Missed study drug dose	
	Randomized treatment switches, if any	
Any change in standard of care (SOC), with pirfenidone or nintedanib therapy	SOC started during study	Treatment policy
	Change in dose of SOC	
	SOC discontinued	All measurements post ICE analyzed
	SOC switch (from pirfenidone to nintedanib or vice-versa)	

Table 2 Primary Estimand Analysis Strategy for Intercurrent Events (cont.)

Intercurrent Event (ICE)		Analysis strategy
Other concomitant treatment	Use of prohibited concurrent medication (Section 4.4.2 in the Protocol)	Treatment policy All measurements post ICE analyzed
Terminal events	Death	Hypothetical strategy Deaths are expected to be rare
Lung transplantation		Hypothetical Strategy Measurements collected after lung transplantation are excluded from the analysis
Hospitalization for COVID-19		Treatment policy strategy All measurements post ICE analyzed

COVID-19=Coronavirus disease 2019; ICE=intercurrent event; IPF=idiopathic pulmonary fibrosis, SOC=standard of care.

1.2 STUDY DESIGN

Study WA42293 is a Phase III, randomized, double-blind, placebo-controlled, pivotal clinical trial designed to confirm the efficacy and safety of zinpentraxin alfa in the treatment of IPF patients with or without concurrent treatment with pirfenidone or nintedanib.

Approximately 658 patients will be randomly assigned on a 1:1 basis to treatment with zinpentraxin alfa at a dose of 10 mg/kg or matched placebo on Days 1, 3, and 5, then one infusion every 4 weeks (Q4W) for 48 weeks. Patients will be evaluated for study eligibility during a screening period of up to 4 weeks. Study treatment will be administered by intravenous (IV) infusion over 50–70 minutes every 4 weeks. If any infusions are missed, repeat loading doses will be required at the next scheduled visit (three doses administered on alternate days). During the placebo-controlled treatment period (defined as Day 1 to Week 52), patients will continue to receive blinded study treatment every 4 weeks to Week 48 and have a final assessment visit at Week 52.

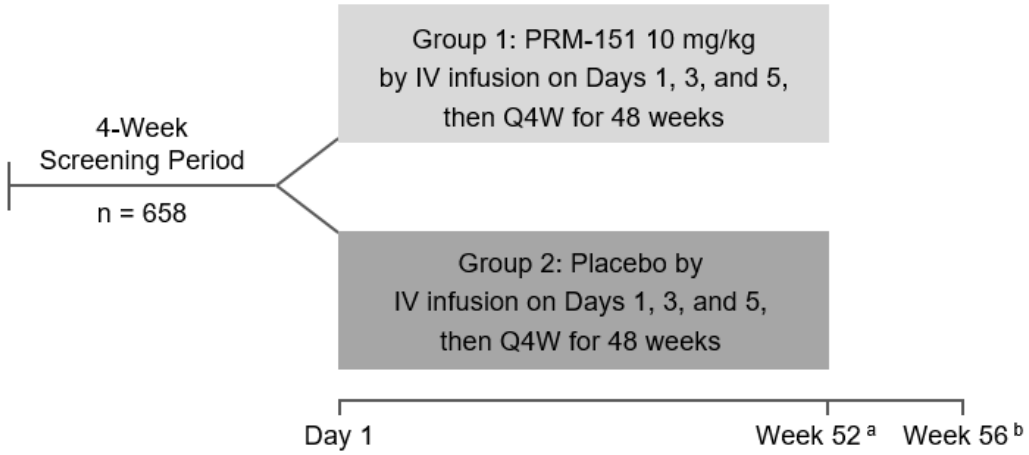
This study will enroll approximately 658 patients globally across all sites. Enrollment will be globally competitive. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase at sites in mainland China, Hong Kong, and Taiwan. The global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

enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subpopulation (see Section 4.7.6 for China subpopulation analyses).

Following participation in this study, patients may be eligible to participate in a separate open-label extension (OLE) study (Study WA42294) to receive treatment with zinpentraxin alfa and further study assessments. Patients who do not enroll in the OLE study will be followed up for an additional 4 weeks (to Week 56, for safety monitoring). The OLE study will also consist of a long-term survival cohort, where patients who do not want further study assessments or treatment can enroll (for long-term collection of survival data only).

The study schema is shown in Figure 1.

Figure 1 Study Schema



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

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

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

1.2.1 Treatment Assignment and Blinding

1.2.1.1 Treatment Assignment

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

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

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

The randomization method implemented in the China extension cohort will be the same as that implemented in the global population, except for the stratification factor for geographic region.

1.2.1.2 Blinding

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

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

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

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

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

1.2.2 Central Review and Adjudication

Central review and adjudication will be performed for clinical and safety data as needed, prior to the efficacy or safety analyses. The membership and procedures of each central review or adjudication will be detailed in a charter or requirements document.

1.2.2.1 Pulmonary Function Tests

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

Carbon monoxide diffusing capacity (DL_{CO}) will be measured according to ATS/ERS guidelines (as referenced in the PFT manual). DL_{CO} will be performed using local equipment, as this will not be provided to study sites.

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

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

1.2.2.2 High-Resolution Computed Tomography

Pulmonary high-resolution computed tomography (HRCT) scans will be reviewed during screening to confirm the IPF diagnosis. Good-quality standard of care scans obtained $\leq$ 12 months prior to screening and in accordance with study image acquisition guidelines can be used for eligibility determination. If scans meeting these conditions are not available, an HRCT scan may be conducted during screening. HRCT scans will be reviewed first by the site radiologist and/or investigator to assess for eligibility.

If the site determines that the patient's HRCT meets IPF diagnostic criteria as specified in the Protocol, the HRCT scans will be sent for central review to confirm eligibility. The blinded central review radiologists will evaluate screening images in accordance with the 2018 Clinical Practice Guidelines by ATS, the ERS, Japanese Respiratory Society (JRS), and the Latin American Thoracic Society (ALAT) (Raghu et al. 2018). Final eligibility will be determined by the central review assessments, inclusive of lung biopsy, if available.

1.2.2.3 Lung Biopsy

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

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

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

1.2.2.5 Assessment for Suspected Anaphylaxis

Assessment of potential anaphylaxis will be conducted at every infusion per the clinical criterion for diagnosing anaphylaxis as described by Sampson et al. (2006) NIAID/FAAN.

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

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

Further details will be provided in the Anaphylaxis Adjudication Charter.

1.2.3 Data Monitoring

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

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The following statistical hypotheses will be tested to demonstrate superiority of zinpentraxin alfa plus standard of care treatment as needed (excluding lung transplantation) compared with placebo plus standard of care treatment as needed (excluding lung transplantation), on lung function for the primary efficacy endpoint:

Null hypothesis H0: the mean change from baseline at Week 52 in FVC mL for patients in the placebo arm is the same as the mean change from baseline at Week 52 in FVC mL for patients in the respective zinpentraxin alfa arm.

Alternative hypothesis H1: the mean change from baseline at Week 52 in FVC mL for patients in the placebo arm is not the same as the mean change from baseline at Week 52 in FVC mL for patients in the respective zinpentraxin alfa arm.

Similar statistical hypotheses will be tested for the key secondary efficacy endpoint: change from baseline at Week 52 in 6-minute walk distance (6MWD).

A fixed-sequence testing strategy will be used for statistical testing of first the primary endpoint then the secondary endpoints in a hierarchical manner to control the overall type I error rate at 0.05 two-sided. See Section 4 for details.

2.2 SAMPLE SIZE DETERMINATION

The purpose of this study is hypothesis testing regarding the effect of zinpentraxin alfa versus placebo.

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

The hypotheses on treatment effect-sizes used for sample-size and power calculations were based on the results of the placebo-controlled period of the PRM-151-202 study, summarized in Table 3.

Table 3 Results of the PRM-151-202 Study on Planned Primary and Key Secondary Endpoints

LS-Means for change from baseline at Week 28 (linear mixed effect models)				
Endpoint	Placebo (N=39) Mean (SE)	zinpentraxin alfa (N=77) Mean (SE)	Difference Mean (SE)	Standardized effect size
FVC (mL)	-242.3 (45.47)	-127.7 (32.86)	114.6 (56.10)	0.40
6MWD (meters)	-33.7 (10.52)	-0.20 (7.59)	33.5 (12.97)	0.51
FVC (% predicted)	-5.40 (0.96)	-2.50 (0.69)	2.80 (1.19)	0.46

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

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

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

To avoid underestimating the power of the study and to enable the opportunity to explore the efficacy in relevant patient subgroups including baseline concomitant IPF medication use, smaller standardized effect-sizes than observed in study PRM-151-202 at Week 28 of 0.25 for FVC mL and FVC % predicted and 0.30 for 6MWD were used for the calculations. In addition, to investigate the impact of increased variability for studies of longer duration, the power for this calculated sample size was assessed in the following way: (a) using the placebo-controlled treatment differences observed at Week 28 as estimates for the Week 52 treatment effects and (b) using the Week 52 standard deviations for the initially randomized zinpentraxin alfa arm from study PRM-151-202, as estimates for the Week 52 common standard deviations. This was performed in order to confirm that the nominal power is at least 80% under these assumptions.

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

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

2.2.2 Robustness of Power and Sample-Size Calculations

In Table 4, power calculations for alternative values of the effect-sizes of the first three endpoints in the fixed-sequence testing are provided.

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

For 6MWD, the study has a high power (0.973) to detect an absolute between group difference of 25 m (considered the minimal clinically relevant difference), corresponding

to a standardized effect-size of 0.30. A smaller effect-size of 0.25, corresponding to an absolute difference of 20.8 m will be detected with a power of 90%.

Table 4 Results of Power Calculations for Different Effect-Sizes and N=658 Patients

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

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

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

2.2.3 Sample Size for the China Subpopulation

This study will initially enroll approximately 658 participants across all sites during the global enrollment phase. After completion of the global enrollment phase, additional participants may be enrolled in an extended China enrollment phase at sites in China, Hong Kong and Taiwan to ensure a total enrollment that is sufficient to support registration in China. The global population will include all participants enrolled during the global enrollment phase (including participants enrolled at National Medical Products Administration (NMPA)-recognized sites during that phase), and the China subpopulation will include all participants enrolled at NMPA-recognized sites (during both the global enrollment phase and the extended China enrollment phase).

3. ANALYSIS SETS

The analysis populations presented in this section are based on patients enrolled during the global enrollment phase of the study and will not include the China extension, unless otherwise specified. The analysis plan for the China extension is presented in Section 4.7.6.

The analysis populations are defined in Table 5.

Table 5 Analysis Populations

Population	Definition
Randomized	All randomized patients
Full analysis set	All randomized patients who received at least one administration (full or partial dose) of study drug and will use the grouping according to the treatment assignment at randomization.
Safety-evaluable	All randomized patients who received at least one administration (full or partial dose) of study drug and will be grouped according to the actual treatment received.
Pharmacokinetic-evaluable	All randomized patients who received at least one administration (full or partial dose) of zinpentraxin alfa and have at least one evaluable postdose PK sample that is above the LLOQ.
Immunogenicity-evaluable	All randomized patients with at least one postdose ADA assessment and will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.
Biomarker-evaluable	All randomized patients who received at least one administration (full or partial dose) of zinpentraxin alfa and have genetic data to enable assessment of MUC5B status. The analysis will group patients according to treatment actually received.

LLOQ = lower limit of quantification; MUC5B = mucin 5B; PRO = patient-reported outcomes.

4. STATISTICAL ANALYSES

The primary analysis will occur when the last enrolled patient from the global enrollment phase has completed the study. Significance testing of the primary and secondary endpoints will account for multiplicity and control family-wise type I error, which is fixed at 0.05 two-sided. The study has one single primary efficacy endpoint (absolute change from baseline at Week 52 in FVC [mL]) and one family of secondary efficacy endpoints that have been ordered in a prespecified sequence, starting with the key secondary endpoint, absolute change from baseline at Week 52 in 6MWD (see Section 4.4).
The planned statistical analysis will control the overall type I error for the testing of these efficacy endpoints by applying a fixed-sequence multiple testing strategy, testing all the endpoints according to the pre-specified order. All hypothesis tests will be two-sided unless otherwise specified.

4.1 GENERAL CONSIDERATION

The efficacy endpoints comprise one primary endpoint (FVC [mL]), one key secondary endpoint (6MWD [m]), a series of other secondary endpoints and other exploratory endpoints. All efficacy analyses will be performed on the FAS population, unless otherwise specified. Participants will be analyzed according to the treatment assigned at randomization by IxRS. Significance testing of the primary and secondary endpoints will account for multiplicity and control family-wise type I error, which is fixed at 0.05 two-sided. All safety analyses will be performed in the safety-evaluable population, unless otherwise specified. Participants will be analyzed according to the treatment they actually received.

In safety analyses, all deaths are included, from all sources, regardless of completeness of death date; participants who died with only a partial death date available will be included. In efficacy analyses, death data from adjudication will be used. If the death date is only partially available, the missing part of the date will be imputed.

For hospitalization in efficacy analyses, the adjudicated date of hospitalization will be used and a partial date will be imputed using the same approach as for death.

4.2 PARTICIPANT DISPOSITION

The number of patients randomized will be tabulated by region, country, study site and treatment arm. The FAS, safety-evaluable, PK-evaluable and PRO-evaluable populations, including numbers of patients in each population, will be summarized. Patient disposition (the number of patients treated and have completed the study) will be tabulated by the treatment arm. Premature treatment discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Definition of Primary Endpoint(s)

The primary efficacy endpoint is the between-group difference in the mean absolute change from Baseline (Dosing Day 1) at Week 52 in FVC (mL). The comparison of zinpentraxin alfa with placebo will be analyzed at a 0.05 two-sided significance level.

All FVC mL measurements that meet the minimal level of quality will be used for the primary analysis, except those recorded after lung transplantation, whatever other intercurrent events might have occurred before that were recorded. No imputation for missing data is planned to be performed for the primary analysis since the primary analysis assumes missing data are MAR and the planned analysis model is unbiased under this assumption.

4.3.2 Main Analytical Approach for Primary Endpoint

Descriptive statistics for the raw values at each visit and the change from baseline at each visit through Week 52 in FVC mL will be computed by treatment group for the FAS population.

The comparison of zinpentraxin alfa with placebo will be carried out via a linear mixed (random coefficient) model at a 0.05 two-sided significance level. Each subject's vector of responses is independent of the other subjects, and within-subject responses are correlated.

The statistical model can be written as follows:

$$Y_{ij} = (\beta_0 + \beta_{0i}) + (\beta_1 + \beta_v Trt_i + \beta_{1i}) * t_{ij} + \beta_s Sex_i + \beta_a Age_i + \beta_h Height_i + \beta_c StrataC_i + \beta_r StrataR_i + \epsilon_{ij}$$

where

- Y_{ij} is the FVC (mL) value for subject i at visit j (including baseline);
- β_0 and β_1 are the intercept and the slope;
- β_{0i} and β_{1i} are the random subject effects for intercept and slope;
- $Trt_i = 0$ if subject i is in the Placebo group and $Trt_i = 1$ if subject i is in the zinpentraxin alfa group;
- β_v is the coefficient for the interaction term of treatment effect and assessment time;
- t_{ij} is the assessment time (continuous in days) for subject i at visit j;
- β_s, β_a and β_h are the coefficients for subject specific demographic variables;
- Sex_i, Age_i , and $Height_i$are the sex (male as the class of reference), baseline age (years) and baseline height (cm) for patient i;
- β_c and β_r are the coefficients for subject specific stratification variables;
- $StrataC_i$ and $StrataR_i$ are the stratification factors on concurrent IPF treatment (no concurrent IPF treatment as the class of reference) and region (Rest of World as the class of reference) for subject i;
- ϵ_{ij} is the within-subject random error for subject i at visit j;
- β_{0i} and β_{1i} are assumed to have a multivariate normal distribution with mean 0 and unstructured covariance matrix;
- ϵ_{ij} are assumed to be independent and normally distributed with mean 0 and variance σ_ϵ^2

If there are convergence problems with the model, the following covariates will continue to be removed from the model (in this order) until convergence is met (1) stratification factor for region, (2) stratification factor for concurrent IPF treatment (3) age, sex, and height. If the model still fails to converge, a random intercept model will be used (no random slope).

The comparison of zinpentraxin alfa with placebo will be carried out by estimating the difference in mean absolute change from baseline at Week 52 between the two treatment arms with 95% CI and p-value.

4.3.3 Sensitivity Analyses for Primary Endpoint

4.3.3.1 Sensitivity Analysis Addressing the Effect of Missing Data After Death due to IPF

To analyze the effect of missing data after death, a rank analysis of covariance (ANCOVA) model will be fit, where patients who die are assigned the worst rank. Specifically, for each patient who survives the duration of the trial, a slope will be calculated from a line fit through their observed FVC assessments. The slopes will then be ranked, assigning the worst rank to patients who die. The rank ANCOVA model will include age, sex, height and ranked baseline score as covariates.

4.3.3.1.1 Sensitivity Analysis Addressing the Effect of Missing Data After Treatment Discontinuation

Patients are expected to continue with study assessments after permanent treatment discontinuation. However, it is possible that patients who discontinue treatment fail to return for their follow-up assessments or discontinue the study, in which case some post-discontinuation data would be missing. Analysis under MAR will implicitly impute these missing values based on all observed data without distinguishing between on-treatment and off-treatment data and may therefore overestimate the treatment effect. Furthermore, the ICE strategy for treatment discontinuation would be a hybrid between a hypothetical and treatment policy strategy, and it becomes unclear what treatment effect is actually being estimated.

More conservative imputation approaches will be implemented to assess the sensitivity of treatment effect estimation and inference to missing data assumptions. The first approach will be to use conditional mean imputation for reference-based imputation of missing data (Wolbers et al. 2022). The imputation model will be an MMRM with baseline outcome, age, sex, height, treatment group, visit and treatment-by-visit interactions as covariates. Missing data for patients in the placebo arm will be imputed under MAR, and missing data for patients in the zinpentraxin alfa arm will be imputed under copy increments in reference. Under this reference-based assumption, patients in the intervention arm who discontinue treatment do not get any further benefit from treatment after discontinuation. The imputed, complete data will be analyzed via ANCOVA, with FVC (mL) slope as the outcome and baseline FVC, age, sex, height and treatment as covariates. Re-sampling based inference for the treatment effect estimate will be obtained via the jackknife.

In addition to the reference-based imputation, a tipping point analysis will be implemented by applying different delta-adjustments for each treatment group to the imputed data to see which combination of delta values tip the primary analysis result.

4.3.3.1.2 Sensitivity Analysis Addressing Non-linearity

To evaluate the impact of assuming a linear disease trajectory, a repeated measures mixed-effects model (MMRM) will be used to estimate the difference in mean change from baseline in FVC (mL) at Week 52. For this sensitivity analysis, only data from scheduled assessments will be used to fit the MMRM. The response variable for the model is change from baseline in FVC (mL). The following variables will be included as model terms: baseline FVC (mL), stratification factors, treatment group, visit and treatment-by-visit interaction. Subject, treatment, and visit will be class variables and the within-subject errors will be assumed to have an unstructured variance-covariance matrix. If the analysis fails to converge, the following covariance structures will be tested: compound symmetry, first-order autoregressive [AR(1)], and Toeplitz. The covariance structure converging to the best fit, based on Akaike's information criterion (AIC), will be used.

The difference in the least squares mean change from baseline between the zinpentraxin alfa and placebo groups will be estimated at each post-baseline visit, as well as 95% CI's and p-values. The MMRM LS means plot with CI's will be made to visualize the estimates.

4.3.4 Supplementary Analyses for Primary Endpoint(s)

4.3.4.1 Subgroup Analyses for Primary Endpoint(s)

The generalizability of primary endpoint results when comparing zinpentraxin alfa to placebo will be investigated by estimating the treatment effect in subgroups based on stratification factors and key baseline demographics, disease characteristics, etc., as listed in Table 6.

Descriptive summaries including number and proportion of patients in each category will be provided overall and by treatment group as appropriate. Summaries of primary endpoint by these subgroups will be provided in forest plots.

Table 6 Subgroup Definitions

Patient Characteristics	Categories
Baseline concomitant medications	– Concurrent use of either nintedanib or pirfenidone treatment – Concurrent use of nintedanib treatment – Concurrent use of pirfenidone treatment – No concurrent treatment
Geographic region	China North America Europe Latin America Rest of World
Age	$<$ 65 years 65 to $<$ 75 years $\geq$ 75 years
Sex	Female Male
zinpentraxin alfa generation	First Generation Second Generation

4.4 SECONDARY ENDPOINTS ANALYSES

If the primary efficacy test on FVC mL is found significant at the alpha level of 0.05 two-sided then the fixed-sequence testing procedure will continue by testing the secondary endpoints in a hierarchical manner as specified below:

1. Absolute change from baseline at Week 52 in 6MWD (m)
2. Absolute change from baseline at Week 52 in FVC% predicted
3. Time to disease progression, defined as time to first occurrence of $\geq$10% absolute decline in % predicted FVC, $\geq$15% relative decline in 6MWD, or death
4. Time to first respiratory-related hospitalization
5. Absolute change from baseline at Week 52 in University of California, San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ)
6. Absolute change from baseline at Week 52 in St. George Respiratory Questionnaire (SGRQ) Total Score
7. Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF, as determined by the Clinical Adjudication Committee
8. Absolute change from baseline at Week 52 in hemoglobin (Hgb)-corrected DL_{CO} % predicted
9. Survival, as measured by all-cause mortality

4.4.1 Key/Confirmatory Secondary Endpoint

The assessment of the key secondary endpoint (6MWD [m]) using the 6MWT is described in Section 4.5.7 of Protocol.

It will be analyzed using the same estimand strategy, descriptive statistics, and model as the primary endpoint (FVC [mL]) in Section 1.1 and Section 4.3.2 and will be analyzed at a 0.05 two-sided significance level.

Subgroup analyses for the primary efficacy endpoint described in Section 4.3.4.1 will be performed for the key/confirmatory secondary endpoint as well using the same descriptive summaries and summaries of treatment effect in forest plots.

4.4.2 Supportive Secondary Endpoint(s)

4.4.2.1 Other Continuous Secondary Endpoints

The other continuous secondary endpoints include:

- absolute change from baseline at Week 52 in FVC% predicted
- absolute change from baseline at Week 52 in Hgb-corrected DL_{CO} % predicted

FVC% predicted will be analyzed using the same estimand strategy, descriptive statistics and model (excluding age, sex and height as covariates) as the primary endpoint (FVC [mL]) in Section 1.1 and Section 4.3.2 and will be analyzed at a 0.05 two-sided significance level.

Visit summary and change from baseline analyses will be performed for Hgb-corrected DL_{CO} % predicted values. Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) of absolute values and changes from baseline at each time point will be presented by treatment arm. Hgb-corrected DL_{CO} % predicted will be analyzed using the same estimand strategy as the primary endpoint (FVC [mL]) in Section 1.1.

A MMRM will be used for comparing the least squares mean change from baseline at Week 52 in Hgb-corrected DL_{CO} % predicted values between treatment arms at a 0.05 two-sided significance level. The model will include baseline value as a covariate, and treatment, time, stratification variables and treatment by time interaction as explanatory variables. Repeated measures over time will be accounted for by an unstructured covariance structure.

The statistical model is as follows:

$$Chg_{ij} = \beta_0 + \beta_t Trt_i + \beta_v Visit_j + \beta_r Trt_i * Visit_j + \beta_b Base_i + \beta_c StrataC_i + \beta_r StrataR_i + \varepsilon_{ij}$$

where

- Chg_{ij} is the change from baseline for subject i at visit j;
- β_0 is the intercept;
- β_t is the coefficient for the treatment effect and Trt_i is the planned treatment for subject i: Trt_i =0 if subject i is assigned to the Placebo group (k = Placebo) and Trt_i=1 if subject i is assigned to the zinpentraxin alfa group;
- β_v is the coefficient for the visit effect and $Visit_j$ is the categorical visit;
- β_r is the coefficient for the interaction term between treatment and categorical visit and $Trt_i * Visit_j$ is the interaction term between treatment and categorical visit;
- β_b is the coefficient for the baseline measure and $Base_i$ is the baseline measure for subject i;
- β_c and β_r are the coefficients for subject specific stratification variables;
- $StrataC_i$ and $StrataR_i$ are the stratification factors on concurrent IPF treatment (no concurrent IPF treatment as the class of reference) and region (Rest of World as the class of reference) for subject i;
- ε_{ij} is the random error for subject i at visit j.

If the analysis fails to converge, the following covariance structures will be tested: compound symmetry, first-order autoregressive [AR(1)], and Toeplitz. The covariance structure converging to the best fit, based on Akaike's information criterion (AIC), will be used.

The least squares mean estimates of the mean change from baseline and the difference between the two treatment arms at each post-baseline visit will be provided with 95% CIs and p-values.

4.4.2.2 PRO Secondary Endpoints

The PRO secondary endpoints are listed below:

- Change from baseline at Week 52 in UCSD-SOBQ score
- Change from baseline at Week 52 in SGRQ total score

The PRO secondary endpoints will be analyzed using the same estimand strategy, descriptive statistics and model as Hgb-corrected DL_{CO} % predicted in Section 4.4.2.1 and will be analyzed at a 0.05 two-sided significance level.

4.4.2.3 Time-to-Event Secondary Endpoints

The time-to-event secondary endpoints are listed below:

- Time to disease progression, defined as time to first occurrence of ≥ 10% absolute decline in % predicted FVC, ≥15% relative decline in 6MWD, or death
- Time to first respiratory-related hospitalizations (defined as non-elective hospitalizations due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF, as determined by the Clinical Adjudication Committee)
- Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF, as determined by the Clinical Adjudication Committee
- Survival, as measured by all-cause mortality

Descriptive statistics for the frequency of each type of event will be provided. The stratified log rank test (on stratification factors) will be used to compare the time to event endpoints between two treatment arms at a 0.05 two-sided significance level. The Kaplan-Meier plot, median time to event, and their 95% CIs, and a p-value from the log-rank test will be presented. The hazard ratio and its 95% CI will be estimated using a Cox proportional hazards model, adjusting for sex, age, and height. In fitting the Cox model, ties will be handled with the approximate likelihood method of Efron (1977).

Time-to-event will be measured in reference to Baseline Day 1 through the end of study. Patients are considered to be in the placebo-controlled period even if they have discontinued study treatment, if they would still be receiving placebo-controlled study treatment had they not discontinued. For time to first respiratory-related hospitalizations and time to first acute exacerbation of IPF, patients not experiencing an event will be censored at the earliest of the last day known alive, or the last date during the placebo-controlled period (see Section 1.2). For disease progression and survival (all-cause mortality), patients without an event will be censored at the last clinic assessment during the placebo-controlled period.

The estimand strategy for the time-to-event endpoints are summarized below in Table 7.

Table 7 Estimand Analysis Strategy for Intercurrent Events: Time-to-Event Secondary Endpoints

Endpoints	Estimand
• Time to disease progression, defined as time to first occurrence of ≥10% absolute decline in % predicted FVC, ≥15% relative decline in 6MWD, or death	**Population:** see primary endpoint **Treatment:** see primary endpoint **Population-level summary measure:** log rank test and hazard ratio **Intercurrent events:** • Any patients who undergo lung transplantation will be censored at the date of the transplant (hypothetical strategy)
• Survival, as measured by all-cause mortality	**Population:** see primary endpoint **Treatment:** see primary endpoint **Population-level summary measure:** log rank test and hazard ratio **Intercurrent events:** • Any patients who undergo lung transplantation will be censored at the date of the transplantation (hypothetical strategy)
• Time to first respiratory-related hospitalizations (defined as non-elective hospitalizations due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF, as determined by the Clinical Adjudication Committee)	**Population:** see primary endpoint **Treatment:** see primary endpoint **Population-level summary measure:** log rank test and hazard ratio **Intercurrent events:** • Deaths are expected to be infrequent, but in case of occurrence, they will be treated as disease progression and counted as event of interest (composite strategy) • Any patients who undergo lung transplantation will be censored at the date of the transplantation (hypothetical strategy)
• Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF, as determined by the Clinical Adjudication Committee	**Population:** see primary endpoint **Treatment:** see primary endpoint **Population-level summary measure:** log rank test and hazard ratio **Intercurrent events:** • Deaths are expected to be infrequent, but in case of occurrence, they will be treated as disease progression and counted as event of interest (composite strategy) • Any patients who undergo lung transplantation will be censored at the date of the transplantation (hypothetical strategy)

6MWD = 6-minute walk distance; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis.

4.5 EXPLORATORY ENDPOINT(S) ANALYSIS

The exploratory efficacy endpoints are:

- Absolute change from baseline at Week 52 in FVC% predicted and FVC (mL), by baseline concomitant medication stratum
- Absolute change from baseline at Week 52 in FVC% predicted and FVC (mL), by mucin 5B (MUC5B) risk allele positive or negative status
- Absolute change from baseline at Week 52 in 6MWD (m), by baseline concomitant medication stratum
- Proportion of patients who progress on the UCSD-SOBQ, as indicated by an increase in score of 10 points or greater
- Proportion of patients who progress on the SGRQ total score, as indicated by an increase in score of 7 or greater
- Change from baseline to Week 52 in SGRQ Individual Domains (Symptoms, Activity, and Impacts) Score
- Proportion of patients who progress on the SGRQ Symptoms Domain, as indicated by an increase in score of 8 or greater
- Proportion of patients who progress on the SGRQ Activity Domain, as indicated by an increase in score of 5 or greater
- Proportion of patients who progress on the SGRQ Impacts Domain, as indicated by an increase in score of 7 or greater
- Absolute change from baseline at Week 52 in quantitative imaging analysis parameters of HRCT scan of the thorax
- Length of hospital stay for respiratory-related hospitalizations
- Total time in intensive care units due to respiratory causes
- Unscheduled outpatient clinic/urgent care/emergency room utilization related to respiratory events
- Number of acute exacerbations during the 52 weeks, as determined by the Clinical Adjudication Committee
- Survival as measured by IPF-related mortality
- Survival as measured by respiratory-related mortality
- Disease progression and subsequent start of oxygen supplementation
- Change in PFT parameters (FVC, DL_{CO}) or 6MWD from baseline at Week 52 between SARS-CoV2 antibody positive compared with negative patients (present at baseline)
- Change in PFT parameters (FVC, DL_{CO}) or 6MWD from baseline at Week 52 in patients who develop SARS-CoV2 antibodies during treatment (not present at baseline)
- Absolute change from baseline at Week 52 in FVC (mL) by selected countries

In addition, the following endpoint will be explored to evaluate health status utility scores of patients treated with zinpentraxin alfa plus standard of care treatment:

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

Change-from-Baseline Exploratory Endpoints: FVC, 6MWD, DL_{CO}, EQ-5D-5L VAS

The endpoints on FVC, 6MWD and DL_{CO} will be analyzed and summarized with use of the same methods as the change from baseline endpoints in Section 4.3.2, Section 4.4.1, and Section 4.4.2.1, unless otherwise specified.

The EQ-5D-5L VAS endpoint will be analyzed and summarized with use of the same methods as the change from baseline endpoints in Section 4.4.2.2.

Change-from-Baseline Exploratory Endpoints: HRCT

Descriptive statistics for the raw values at each visit and the change from baseline to Week 52 will be computed by the treatment group for the quantitative HRCT imaging analysis parameters.

Proportion of progressors: SGRQ, UCSD-SOBQ

The proportion of progressors at Week 52 will be estimated by treatment group with 95% CIs using a standardized regression estimator, adjusting for baseline score and baseline concurrent IPF treatment.

Acute Exacerbation of IPF Endpoints

Descriptive statistics for continuous variables will be prepared by treatment group for the total number and rate (per year) of acute or suspected exacerbations during the 52 weeks.

Time-to-Event Exploratory Endpoints

These endpoints will be analyzed and summarized with use of the same methods for the time-to-event secondary endpoints, unless otherwise specified.

Healthcare Utilization Exploratory Endpoints

Descriptive statistics for continuous variables will be prepared for:

- Length of hospital stay in days for respiratory-related hospitalizations
- Total time in intensive care units in days due to respiratory causes

- Unscheduled outpatient clinic/urgent care/emergency room utilization related to respiratory events

Impact of SARS-CoV2 Antibody

Descriptive statistics will be prepared for:

- Change in PFT parameters (FVC, DL_{CO}) or 6MWD from baseline at Week 52 between SARS-CoV2 antibody positive compared with negative patients (present at baseline)
- Change in PFT parameters (FVC, DL_{CO}) or 6MWD from baseline at Week 52 in patients who develop SARS-CoV2 antibodies during treatment (not present at baseline)

4.6 SAFETY ANALYSES

Safety analyses will be based on all patients who received at least one administration (full or partial dose) of randomized study drug, with patients grouped according to the actual treatment received. Safety summaries will be presented by the treatment arm for all treated patients.

Safety will be assessed through descriptive summary of exposure to study treatment, seriousness and severity of AEs and adverse events of special interest (AESIs), changes in laboratory test results, death, discontinuation from study treatment, ECG and vital signs. These summaries will be produced for the entire study period (placebo-controlled study treatment period and safety follow-up period for patients not entering the open label extension study).

4.6.1 Extent of Exposure

Extent of exposure to study drug (zinpentraxin alfa or placebo) will be summarized descriptively (mean, standard deviation, median, range, and proportions where appropriate) for the following measures:

- Number of patients exposed
- Treatment duration (weeks), measured from date of first administration at Baseline Day 1
- Cumulative number of infusions = total number of non-zero infusions
- Cumulative volume of infusion received = total volume of non-zero infusions
- Number of missed infusions
- Number of patients receiving reloading infusions
- Number of infusion cycles, defined as either up to 3 loading or reloading infusion or 1 regular infusion

Extent of exposure to zinpentraxin alfa will also be summarized by drug generation using the above measures.

Exposure to concurrent use of pirfenidone or nintedanib will also be summarized descriptively by treatment group.

4.6.2 Adverse Events

All verbatim ("investigator-reported") AE terms will be assigned a standardized term (the "preferred term") and a superclass term using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and AE severity will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 scale. A by-patient AE data listing including onset study day, duration, preferred term, treatment, severity, relationship to treatment, treatment for AE, action taken, and outcome will be provided.

All AEs, serious adverse events (SAEs), AEs leading to death, AESIs, and AEs leading to study treatment discontinuation that occur during or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by preferred term and severity grade as appropriate. An exacerbation or worsening of a pre-existing condition will be considered treatment-emergent only if the most extreme intensity is greater than the intensity at baseline (i.e., the intensity for a given AE increases and its end date is on or after the date of the first dose). For events of varying severity, the highest grade will be used in the summaries. Listings of AEs, SAEs, and AESIs will also be produced. Any non-treatment emergent SAEs will also be listed separately.

Summary tables of the cumulative incidence of safety outcomes will be provided for the treatment and placebo arms independently. Safety outcomes of interest include, but are not limited to:

- AEs and SAEs of any grade
- AEs (any grade) with a difference in incidence between the treatment and placebo arm
- AEs by highest NCI CTCAE v.5.0 grade
- Severe AEs (NCI CTCAE v.5.0 Grade 3 or above)
- AEs leading to death
- AEs leading to study treatment discontinuation
- AEs leading to drug interruption
- AEs leading to withdrawal from study
- Treatment related AEs and SAEs
- AESIs
- Common AEs, i.e., those occurring in at least 5% of patients in either arm
- Suspected Infusion Related Reaction (all grades)

Summaries of safety data by baseline concurrent anti-fibrotic therapy and zinpentraxin alfa drug generation will be provided as appropriate.

The within-arm cumulative incidence and the difference in cumulative incidence between arms, along with the 95% CIs, will be summarized in a forest plot for the following safety outcomes: all AEs, all severe AEs, all SAEs, all AEs leading to treatment discontinuation, all AEs determined to be related to study drug, deaths, and the most frequent individual AEs (by preferred term).

Deaths and cause of death will be summarized and a listing of patients who died during the study will be provided.

Summaries of confirmed or suspected COVID-19 AEs and AEs associated with COVID-19 will also be provided.

A listing of all pregnancies will be presented.

AESIs for this study are as follows:

AESIs related to drug development in general:

- Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.4.5.7 of the Protocol) or if the patient is reported to have the preferred term of ‘drug-induced liver injury’
- Suspected transmission of an infectious agent by the study drug, as defined below:

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

AESIs relevant to zinpentraxin alfa:

- Suspected Infusion Related Reaction with NCI CTCAE Grade $\geq$2: The risk of IRR associated with zinpentraxin alfa is inherent in it being the recombinant form of a naturally occurring human protein. The subset of the potential risk of IRR (Grade $\geq$2) has been categorized as drug specific AESI for close monitoring. Infusion Related Reaction includes all the cases if meet both the following criteria: (i) any events onset during the infusion or within 24 hours from the end of study infusion (ii) causality: not unrelated (related or missing). However, further analysis

will be performed to identify true cases of IRR based on medical judgement and confirmation provided by the investigators.

- Suspected anaphylactic or hypersensitivity reactions (all grades): Anaphylactic and hypersensitivity reactions are considered potential risk for all biologic medications including zinpentraxin alfa. Potential cases of anaphylactic, anaphylactoid, and hypersensitivity reactions will be identified and sent for adjudication by an independent Anaphylaxis Adjudication Committee (see Section 1.2.2.5). Events will be identified using the Standardized MedDRA Query (SMQ Wide) 'Anaphylactic reaction' and MedDRA gastrointestinal symptoms event terms consistent with Sampson criteria. In addition, all cases flagged by the investigator as an AESI under the criterion 'Suspected anaphylactic or hypersensitivity reactions' or with an AE term of "anaphylaxis", "hypersensitivity" or for which an investigator has assessed that the event represents "known or suspected" anaphylaxis will be considered for adjudication. Members of the AAC review blinded data to adjudicate cases as anaphylaxis per Sampson's Criteria and for relatedness to study drug. A detailed description of the process for identification of potential events and data flow is provided in the AAC Charter. Events adjudicated by the AAC as meeting Sampson's Criteria for anaphylaxis and relatedness to study drug will be summarized. Additionally, a listing of all possible cases of anaphylaxis will be produced.
- Acute or suspected exacerbation of IPF (all grades): Acute exacerbation of IPF is defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality, marked by the following diagnostic criteria (Collard et al. 2016):
  - Previous or concurrent diagnosis of IPF
  - Acute worsening or development of dyspnea typically <30 days in duration
  - Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP pattern
  - Deterioration not fully explained by cardiac failure or fluid overload
- Acute exacerbations of IPF are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found (e.g., infection, post-procedural/postoperative, drug toxicity, aspiration). There is no evidence to suggest acute or suspected exacerbation of IPF is a risk associated with zinpentraxin alfa. This was categorized as an AESI based on the feedback received through the Voluntary Harmonization Procedure.
- An independent, blinded Clinical Adjudication Committee review all available data for all potential cases of acute exacerbations of IPF. The committee determines if the reported events meet the criteria of an acute exacerbation of IPF or a suspected acute exacerbation. Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet all four diagnostic criteria owing to the

missing computed tomography data are termed “suspected acute exacerbations of IPF”.

The data collected from the already completed Phase I and Phase II trials of zinpentraxin alfa do not suggest that the frequency or nature of the AESIs listed above are serious enough to potentially impact regulatory decision-making.

4.6.3 Adjudicated Anaphylactic and Hypersensitivity Reactions

Anaphylaxis and hypersensitivity events as adjudicated by the Anaphylaxis Adjudication Committee will be summarized descriptively. Listing of treatment emergent adverse events of anaphylaxis and hypersensitivity as defined above and their assessment by an Independent Anaphylaxis Adjudication Committee as per the Anaphylaxis Adjudication Committee charter will be produced.

4.6.4 Laboratory Data

Descriptive summaries of laboratory values at baseline, by visit, and change from baseline throughout the study will be tabulated by each treatment arm. Highest NCI CTCAE v.5.0 grade post-baseline will also be reported and shift tables from baseline to worst value during the study post-baseline will be presented by each treatment arm.

Summaries will be analyzed for the following parameters: hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, and differential counts [lymphocytes, eosinophils, neutrophils, monocytes, and basophils]), serum chemistries and liver function tests (LFTs) (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, C-reactive protein [CRP], eGFR) and urinalysis (pH, specific gravity, glucose, protein, ketones, blood, sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

Proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm as appropriate for the parameters listed above.

A Hy’s law analysis will be provided. The potential Hy’s law quadrant is defined as ALT or AST increases above 3-fold the upper limit of normal (ULN) with concomitant total bilirubin increases above 2-fold the ULN or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered as an indicator of severe liver injury (as defined by Hy’s Law).

Visual plots (box plots or line plots) will be used to display selected laboratory parameters over time/by visit where appropriate.

4.6.5 Vital Signs

Values, along with change from baseline, will be summarized using descriptive statistics for each vital sign parameter.

Summary statistics on absolute values and their change from baseline for all observed vital signs (respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, oxygen saturations, and temperature) will be presented over time by treatment group. Baseline is defined as the last assessment prior to treatment.

4.6.6 ECGs

A shift table of qualitative ECG assessments will be produced.

4.6.7 Other Safety Endpoints

Summaries of safety data by ADA status will be provided as appropriate. See Section 4.7.5 for more details on ADA status.

4.7 OTHER ANALYSES

4.7.1 Summaries of Conduct of Study

Eligibility criteria deviations and other major protocol deviations will be summarized.

The impact of COVID-19 will be assessed by including major protocol deviations related to COVID-19 and by summarizing COVID-19 related intercurrent events by treatment arm.

Compliance analysis will be performed for the overall UCSD-SOBQ and SGRQ questionnaires. Compliance rates will be summarized by number and proportion of patients among those expected to complete the UCSD-SOBQ or SGRQ at each time point.

4.7.2 Summaries of Treatment Group Comparability

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

Demographic and baseline characteristics (including, but not limited to, age, sex, race/ethnicity, concomitant IPF medication use, comorbid illnesses, and pulmonary function) will be summarized overall for the FAS population and by treatment group using descriptive statistics as appropriate.

Compliance with study drug will be computed for each patient as the proportion of prescribed study drug actually taken for the safety population.

Proportions of patients taking each concomitant medication will be provided for the safety population.

Medical history will be summarized using summary statistics, reporting the proportion of patients with at least one medical condition and the total number of medical conditions based on the safety population.

4.7.3 Pharmacokinetic Analyses

Summary tables for plasma concentration of zinpentraxin alfa (mean, standard deviation, %CV, geometric mean, % CV of geometric mean, median, minimum, and maximum) will be produced by visit, treatment arm, and drug generation. As more intensive PK data are collected in patients enrolled in China (and Hong Kong and Taiwan, if applicable) and Japan, summary tables will be produced for these patients separately (see Section 4.7.6 for details on the analyses of China and Japan subpopulations).

Individual patient data and descriptive statistics (i.e., median and interquartile range) will be plotted by visit for each treatment arm.

Exploratory PK analyses to evaluate potential relationships between drug exposure and the efficacy and safety of zinpentraxin alfa will be performed. These analyses will be presented in a separate report and the results will be reported separately as appropriate.

4.7.4 Biomarker Analyses

Exploratory biomarker analyses will be performed to identify and/or evaluate biomarkers in the context of drug activity, efficacy, PK, safety, and/or immunogenicity endpoints. These analyses will be detailed in the Biomarker Analysis Plan and the results will be reported separately.

4.7.5 Immunogenicity Analyses

The following summaries will be provided by the treatment group:

- Number and proportion of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence)
- Number and percentage of patients with treatment-induced, treatment-enhanced and treatment unaffected ADAs
- Drug concentration at ADA collection timepoints

A by-patient listing of ADA status will be provided.

When determining post-baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA

positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, and PK, will be analyzed and reported via descriptive statistics. ADA status will also be reported by drug generation.

4.7.6 Analyses of China and Japan Subpopulations

If applicable, a separate analysis will be performed for the China subpopulation, where data from all participants enrolled at sites in mainland China, Hong Kong, and Taiwan (during both the global enrollment phase and the extended China enrollment phase) will be combined and summarized. Similar analysis will be conducted for the Japan subpopulation. These analyses will be detailed in a separate analysis plan. Data from the China extension cohort will not be included in the primary analysis of the main study.

All analyses described in this section will include data from the Japan subpopulation and all data from the China subpopulation collected up to the clinical cutoff date for the China subpopulation analysis as defined in Section 1.2.

The analysis population for the China subpopulation analyses includes all participants enrolled at sites in mainland China, Hong Kong, and Taiwan. The Japan subpopulation includes all participants enrolled in Japan. Data for the China and Japan subpopulations will be analyzed using the same statistical methods as described in Section 4.1 to Section 4.6 when data allow. In addition, key PK and ADA data for the China and Japan subpopulations will be summarized.

The PK parameters for zinpentraxin alfa in plasma will be estimated as appropriate for each subject profile in the China and Japan subpopulations by non-compartmental analysis methods using Phoenix WinNonlin software (v8.3 or later, Certara USA, Inc.).

Plasma PK parameters definitions are as below:

- C_{max}: maximum observed concentration
- T_{max}: time to maximum observed concentration
- AUC_{0-t}: area under the concentration-time curve from hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
- $AUC_{0-\infty}$: area under the concentration-time curve extrapolated to infinity, calculated using the formula:

$$AUC_{0-\infty} = AUC0\text{-}t + C_t/\lambda_z$$

where C_t is the last measurable concentration and λ_z is the terminal elimination rate constant

- $\%AUC_{extrap}$: percentage of area under the concentration-time curve that is due to extrapolation from the last measurable concentration to infinity
- λ_z: terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
- $t_{1/2}$: terminal elimination half-life (whenever possible), where $t_{1/2} = (\ln 2)/\lambda_z$
- CL: systemic clearance
- V: volume of distribution

Other parameters may be added as appropriate. PK parameters analysis will use actual times as recorded on the eCRF.

Estimates for PK parameters will be listed and summarized (mean, standard deviation, coefficient of variation mean, geometric mean, coefficient of variation geometric mean, median, minimum, and maximum).

Additional exploratory PK analyses will be conducted as appropriate. Exploratory PK analyses to evaluate potential relationships between drug exposure and the efficacy and safety of zinpentraxin alfa might be described in a separate document and presented in a separate report.

4.7.7 Other Analyses

SARS-CoV-2 serology will be summarized descriptively by time point and treatment group.

4.8 INTERIM ANALYSES

4.8.1 Planned Interim Analysis

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

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

The futility analysis will be based on the following endpoint:

- Absolute change from baseline to Week 28 in FVC (mL)

The difference in mean absolute change from baseline to Week 28 in FVC (mL) between the two treatment arms will be estimated using a linear mixed-effect model with random intercept and random slope, with FVC mL measured at each timepoint (including baseline) as the dependent variable, stratification factors, age, sex, height, and treatment by time interaction as fixed effects, and subject and time as random effects.

The full analysis set (FAS) is defined as all randomized patients who received at least one administration (full or partial) of study drug. A subset of the FAS will be used for the interim futility analysis. Only patients in the FAS with an expected Week 28 visit by the data cutoff date will be used for the futility analysis and will be grouped according to their treatment assignment at randomization. Patients contributing data to the futility analysis may have assessments beyond Week 28. Assessments collected after Week 28 will also be included in the futility analysis. No missing data will be imputed for the interim analysis. Measurements collected after lung transplantation will be excluded from the analysis.

The criterion to declare futility will be based on the estimated difference in FVC decline between PRM-151 and placebo. In particular, the iDMC will declare the study futile if the following condition is met:

- The estimated difference in mean absolute change from baseline at Week 28 in FVC (mL) between rhPTX-2 and placebo treated patients is less than 10 mL

The data cutoff date (the date by which assessments that have occurred will be included in the futility analysis) is the date by which 40% of patients (according to planned total sample size) are scheduled to have completed their Week 28 visit. For these first 40% of patients, all assessments that occur before or on the data cutoff date will be included in the analysis, including assessments collected after the Week 28 visit.

All outputs for the futility analysis will be produced by the iDCC on unblinded data and will be reviewed during the futility analysis meeting by the iDMC only.

4.8.2 Optional Interim Analysis

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

If an interim efficacy analysis is conducted, the Sponsor will remain blinded. The interim efficacy analysis will be conducted by an external statistical group and reviewed by the

iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter. If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology (DeMets and Lan 1994).

5. SUPPORTING DOCUMENTATION

Refer to Appendix 1 below for details.

Appendix 1 Changes to Protocol-Planned Analyses

The following are the major changes to the planned analyses specified in the Study WA42293 protocol, Version 5. These are captured in the following sections of this SAP:

- Section 1.1 and Section 4.5 were updated to simplify exploratory endpoints and to clarify primary and secondary endpoints.
- Section 1.1 was updated to amend the ICE strategy for death for the primary endpoint analysis.
- Section 4.3.2 was updated to show approaches used in case of model non-convergence.
- Section 4.4.2 was updated for the analysis method for Hgb-corrected DL_{CO} % predicted.

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