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

NCT Number: NCT04594707

Document Dates: SAP Version 1: 24-August-2022

STATISTICAL ANALYSIS PLAN

STUDY TITLE: A PHASE III OPEN-LABEL EXTENSION STUDY TO EVALUATE LONG-TERM SAFETY AND EFFICACY OF PRM-151 IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF)

STUDY NUMBER:	WA42294
STUDY NAME:	STARSCAPE OLE
VERSION NUMBER:	1
ROCHE COMPOUND:	Recombinant human pentraxin-2 (rhPTX-2; PRM-151; RO7490677) [Zinpentraxin Alfa]
EUDRACT NUMBER:	2020-001429-30
IND NUMBER:	110,774
NCT NUMBER:	NCT04594707
PLAN PREPARED BY:	[redacted], Ph.D.

STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR:	F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
DATE FINAL:	See electronic signature on the last page of this document.

STATISTICAL ANALYSIS PLAN VERSION HISTORY

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

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	See electronic signature on the last page of this document	Version 4, 28 April 2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWD	6-minute walk distance
6MWT	6-minute walk test
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
COVID-19	Coronavirus Disease 2019
DL_{CO}	carbon monoxide diffusing capacity
eCRF	electronic Case Report Form
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
EuroQol	European Quality of Life Scale
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FVC	forced vital capacity
HRCT	high-resolution computed tomography
iDMC	independent Data Monitoring Committee
IPF	idiopathic pulmonary fibrosis
IRR	infusion-related reaction
IV	intravenous
IxRS	interactive voice/web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OLE	open-label extension
PD	pharmacodynamic
PFTs	pulmonary function tests
PK	pharmacokinetic
PRO	patient-reported outcomes
PT	Preferred Term
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
SpO2	oxygen saturation levels
TEAE	treatment-emergent adverse event
UCSD-SOBQ	University of California, San Diego Shortness of Breath Questionnaire
ULN	upper limit of normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details on the study design, outcome measures, and statistical analysis plan for Study WA42294 (STARSCAPE OLE). 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 wherever possible. The analyses and endpoints specified in this document supersede the analysis plan described in the study protocol.

1.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the long-term safety, efficacy, and pharmacokinetics of open-label zinpentraxin alfa in patients with idiopathic pulmonary fibrosis (IPF). Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Safety Objective	Corresponding Endpoints
• To confirm the long-term safety and tolerability of 10 mg/kg of zinpentraxin alfa administered every 4 weeks (Q4W) via IV infusion plus standard of care (SOC) treatment	• Incidence and severity of adverse events (AE), with severity determined according to the 5-point severity scale (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI CTCAE, v.5.0]) • Incidence and severity of infusion-related reactions (IRRs) and other AEs of special interest • Proportion of patients permanently discontinuing study treatment due to AEs • Change from baseline in targeted clinical laboratory test results
Efficacy Objective	**Corresponding Endpoints**
• To assess the long-term efficacy of 10 mg/kg zinpentraxin alfa plus SOC (excluding lung transplantation) administered Q4W via IV infusion	• Annual rate of change in FVC (mL) • Annual rate of change in 6-minute walk distance (6MWD) • Annual rate of change in FVC% predicted • Annual rate of change from baseline in carbon monoxide diffusing capacity (DL_{CO}) • Time to disease progression, defined as time to first occurrence of ≥10% absolute decline in % predicted FVC, ≥5% relative decline in 6MWD, or death • Survival, as measured by all-cause mortality • IPF-related mortality and respiratory-related mortality

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective(s)	Corresponding Endpoints
• To assess the long-term efficacy of 10 mg/kg zinpentraxin alfa plus SOC (excluding lung transplantation) administered Q4W via IV infusion	• Change from baseline in University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ) • Change from baseline in St. George Respiratory Questionnaire (SGRQ) Total Score • Time to first respiratory-related hospitalizations (defined as non-elective hospitalizations due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF, as determined by Adjudication Committee) • Time to first acute exacerbation of IPF • See Section 5.5
• To explore additional measures and subgroups of interest including concurrent use of IPF treatment and geographic region	• See Section 5.6.6
• To assess the long-term impact of 10 mg/kg zinpentraxin alfa plus SOC on healthcare utilization for respiratory events.	• 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

Table 1 Objectives and Corresponding Endpoints (cont.)

Pharmacokinetic Objective	Corresponding Endpoint
• To characterize pharmacokinetics of zinpentraxin alfa in patients with IPF (from Cohort A, and Cohort B, who are enrolled in the WA42293 study prior to 1 June 2022)	• Plasma concentrations of zinpentraxin alfa at specified timepoints
Exploratory Pharmacokinetic Objective	**Corresponding Endpoint**
• To evaluate the potential relationship between drug exposure and the efficacy and safety of zinpentraxin alfa (from Cohort A, and Cohort B, who are enrolled in the WA42293 study prior to 1 June 2022)	• Relationship between PK for zinpentraxin alfa and efficacy endpoints • Relationship between PK for zinpentraxin alfa and safety endpoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to zinpentraxin alfa in patients with IPF (from Cohort A, and Cohort B, who are enrolled in the WA42293 study prior to 1 June 2022)	• Prevalence of ADAs at baseline and incidence of ADAs during the study
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to zinpentraxin alfa in patients with IPF (from Cohort A, and Cohort B, who are enrolled in the WA42293 study prior to 1 June 2022)	• Relationship between ADA status and efficacy, safety, or PK endpoints

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Biomarker Objective	Corresponding Endpoint
• To identify and/or evaluate biomarkers that can provide evidence of zinpentraxin alfa activity and the duration of that activity (i.e., pharmacodynamic biomarkers), are associated with acquired resistance to zinpentraxin alfa, are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), or can increase the knowledge and understanding of disease biology and drug safety (Cohort A and Cohort B)	• Relationship between biomarkers in blood listed in Protocol Section 4.5.10 (Laboratory, Biomarker, and Other Biological Samples) and safety, efficacy, PK, immunogenicity, or other biomarker endpoints
Exploratory Health Status Utility Objective	**Corresponding Endpoint**
• To evaluate health status utility scores of patients treated with zinpentraxin alfa plus SOC	• Annual rate of change in EuroQol 5 Dimension, 5 Level Questionnaire (EQ 5D 5L) index based, and visual analog scale (VAS) scores

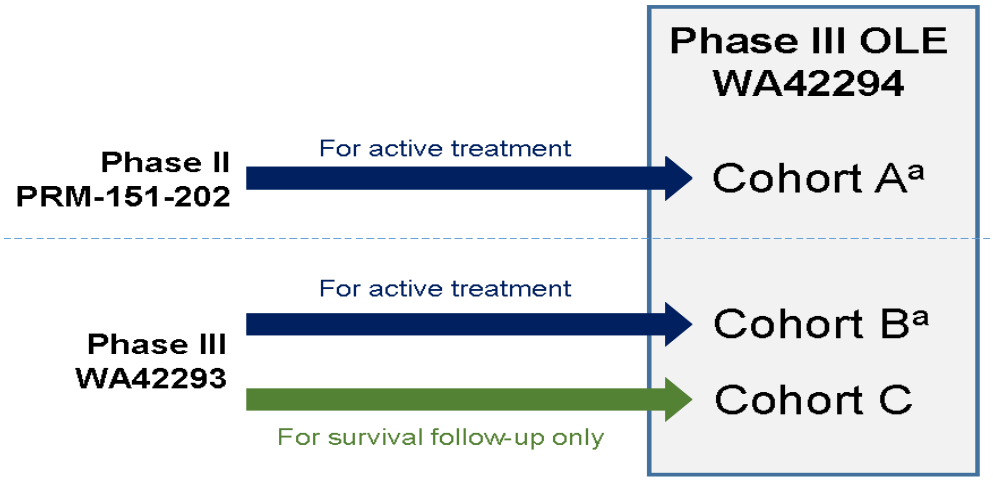
ADA=anti-drug antibody; AE = adverse event; DL_{CO}=carbon monoxide diffusing capacity; EuroQol = European Quality of Life Scale; FVC=forced vital capacity; IRR=infusion-related reaction; PK = pharamcokinetic; zinpentraxin alfa = Recombinant human pentraxin-2 (PRM-151, RO7490677).

1.2 STUDY DESIGN

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

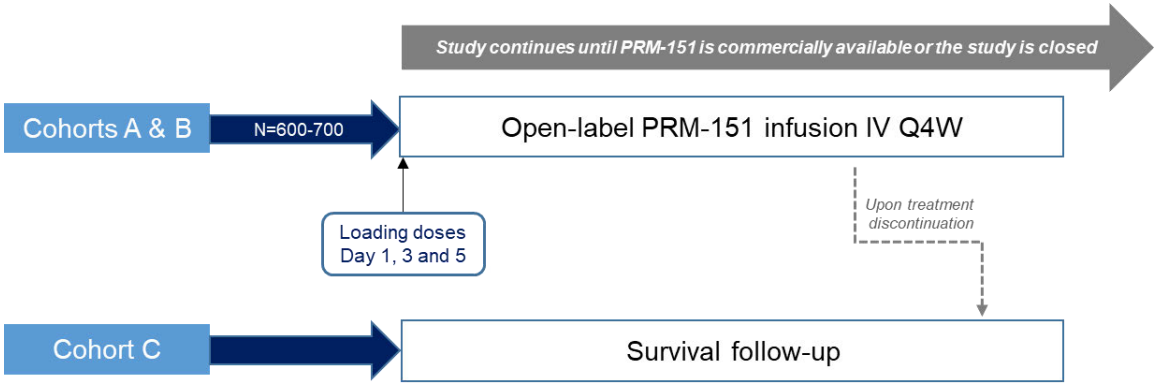
The study schema is shown in Figure 2.

Figure 1 Cohort Allocation



[a] Only Cohorts A and B receive active treatment.
OLE = open-label extension.

Figure 2 Study Schema



IV=intravenous; Q4W=every 4 weeks.
PRM-151 to be read as zinpentraxin alfa or rhPTX-2.

Patients meeting the eligibility criteria for the study will receive zinpentraxin alfa 10 mg/kg every 4 weeks (Q4W). Throughout the study, patients will be monitored for safety by collection of adverse events (AEs; both serious and non-serious) and by regular physical exam and safety laboratory assessments.

Efficacy will be evaluated through assessment of functional capacity as measured by forced vital capacity (FVC), 6-minute walk distance (6MWD), other pulmonary function tests (PFTs), and assessment of patients with respiratory events leading to hospitalizations, progression of disease, or acute IPF exacerbations.

Patient reported outcomes (PRO) will be assessed using the St. George Respiratory Questionnaire (SGRQ), University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ), and European Quality of Life Scale (EuroQol) 5-Dimension, 5-Level Questionnaire (EQ-5D-5L).

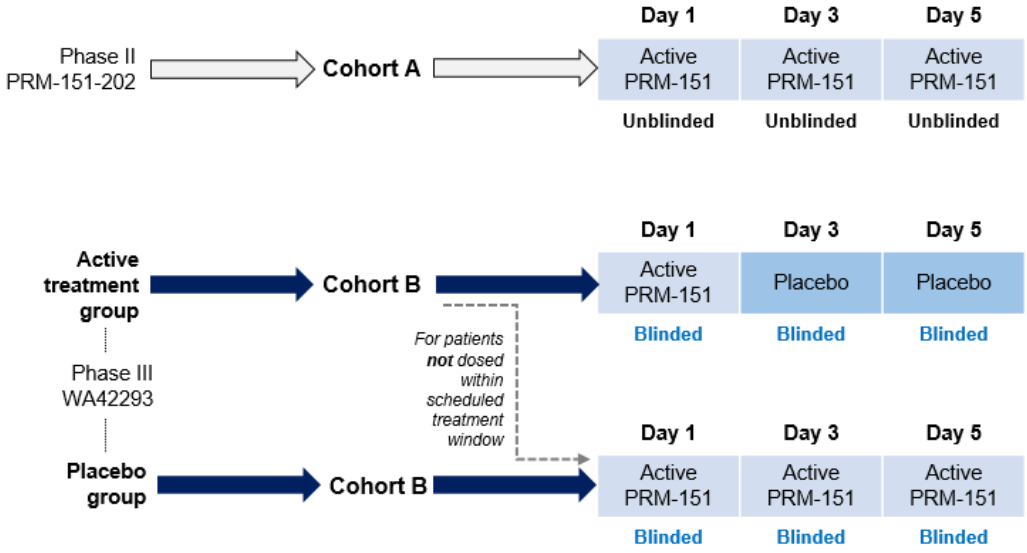
Dyspnea, fatigue, and blood oxygen saturation levels (SpO2) will be assessed based on measurements taken during the 6-minute walk test (6MWT). High-resolution computed tomography (HRCT) of the chest will be assessed for changes between Week 52 from Study WA42293 to Week 52 (OLE) and Week 104 (OLE). Treated patients will be followed-up until the end of the study period, unless the patient withdraws consent for follow-up or death occurs.

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

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

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

Figure 3 Initial Loading Doses for Cohorts A and B



PRM-151 to be read as zinpentraxin alfa.

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

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

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

1.2.1 Treatment Assignment

In this study all patients in Cohorts A and B will receive zinpentraxin alfa.

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

For patients enrolling in Cohort B:

- Patients previously randomized to placebo in Study WA42293 will receive three loading doses on Days 1, 3, and 5 in a blinded fashion. All three doses will contain zinpentraxin alfa.

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

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

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

1.2.2 Independent Review Facility

An Anaphylaxis Adjudication Committee, an independent and blinded committee composed of external experts in allergic diseases, will adjudicate all potential anaphylaxis cases reported by investigators to the Sponsor. The committee will assess whether the reported event is a true anaphylaxis event (based on Sampson's criteria) and whether the reported anaphylaxis event is causally related to study treatment. Further details will be provided in the Anaphylaxis Adjudication Charter.

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

1.2.2.1 Assessment for Suspected Anaphylaxis

Assessment of potential anaphylaxis will be conducted at every infusion per the clinical criterion for diagnosing anaphylaxis as described in Appendix 4 of Protocol – Sampson's Criteria for Diagnosing Potential Cases of Anaphylaxis. Patients experiencing suspected anaphylaxis should be managed as per local guidelines. Laboratory samples (serum tryptase, anti-drug antibody [ADA], complement C3) should be collected similarly to infusion-related reactions (IRRs).

All potential anaphylaxis cases reported by investigators to the Sponsor will be subsequently submitted for adjudication to an Anaphylaxis Adjudication Committee

composed of external experts in allergic diseases. The committee will assess whether the reported event is a true anaphylaxis event (based on Sampson's criteria) and whether the reported anaphylaxis event is causally related to zinpentraxin alfa.

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 are outlined in the Anaphylaxis Adjudication Charter.

1.2.2.2 Acute Exacerbations of IPF and Suspected Acute Exacerbations of IPF

Acute exacerbation of IPF is defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality, marked by the following diagnostic criteria (Collard et al. 2016):

- Previous or concurrent diagnosis of IPF
- Acute worsening or development of dyspnea typically <30 days in duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
- Deterioration not fully explained by cardiac failure or fluid overload

Acute exacerbations of IPF are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found (e.g., infection, post-procedural/postoperative, drug toxicity, aspiration).

Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet all four diagnostic criteria owing to missing computed tomography data are termed “suspected acute exacerbations of IPF”.

At each study visit, the investigator will ask directed questions and review the patient file to assess the possibility that the patient experienced an acute IPF exacerbation since the preceding study visit. An acute IPF exacerbation should be reported as an AE of special interest (see Section of the Protocol “Adverse Events of Special Interest [Immediately Reportable to the Sponsor]”) or serious adverse event (SAE) as applicable.

All relevant AE data (summary on clinical course, signs and symptoms; laboratory, lung function and imaging results; and treatment provided, including hospitalizations) relating to the exacerbation must be collected and entered onto the adverse event form. A charter for the Committee describes the process for the data to be reviewed and criteria for defining an IPF exacerbation.

1.2.2.3 Hospitalizations for Respiratory Causes

Hospitalizations for respiratory causes are defined as non-elective hospitalizations due to any respiratory cause, including acute exacerbations of IPF, or suspected acute exacerbations of IPF. All investigator–reported hospitalizations for respiratory causes will be assessed by an independent Adjudication Committee, as described in the charter.

1.2.2.4 Deaths due to Respiratory Causes

All deaths occurring during the study must be recorded. The event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept on the Adverse Event electronic Case Report Form (eCRF).

All investigator-reported deaths that occur in Cohorts A or B will be assessed by an independent Adjudication Committee to determine whether each death was related to IPF, another respiratory cause or an alternative (non-respiratory and non-IPF) cause. Deaths occurring in Cohort C will not be adjudicated.

1.2.2.5 Health Care Utilization for Respiratory Events

The following events will be recorded as health care utilization for respiratory events:

- Unscheduled visits to a healthcare professional/clinic for any respiratory event
- Urgent care or emergency room visits for respiratory events
- Hospitalization days for a respiratory cause, including for exacerbation of respiratory symptoms
- During hospitalization, any stay in ICU, including ICU days

1.2.3 Data Monitoring

An independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate patient safety in Study WA42294 only up until the time the database for primary analysis for Study WA42293 is locked and Study WA42293 is unblinded to the Sponsor (i.e., for the duration of Study WA42293), thereby better ensuring the safety of study patients. Consistent with U.S. Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry 2006), the iDMC will be constituted of independent clinician experts 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.

2. STATISTICAL HYPOTHESES

Because of the non-comparative character of the study, no statistical tests are planned. All efficacy parameters will be summarized descriptively.

3. SAMPLE SIZE DETERMINATION

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

4. 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 patients, unless otherwise specified.

The analysis populations are defined in Table 2.

Table 2 Analysis Populations

Cohort	Population	Definition
Cohort A	Full analysis set (FAS)	All enrolled patients who received at least one administration (full or partial dose) of study drug.
	Safety-evaluable	All enrolled patients who received at least one administration (full or partial dose) of study drug.
	PRO-evaluable	All enrolled patients who received at least one administration (full or partial dose) of study drug and have a baseline and at least 1 post-baseline assessment.
	PK-evaluable	All enrolled patients who received at least one administration (full or partial dose) of study drug and have at least one evaluable post-dose PK sample that is above the lower limit of quantification and with sufficient data to determine plasma concentrations of zinpentraxin alfa at specified timepoints, unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred which may interfere with PK evaluation.
	Immunogenicity-evaluable	All enrolled patients who received at least one administration (full or partial dose) of study drug and have at least one ADA assessment.
	Biomarker-evaluable	All enrolled patients who received at least one administration (full or partial dose) of study drug and have genetic data to enable assessment of MUC5B status.

Table 2 Analysis Populations (cont.)

Cohort	Population	Definition
Cohort B	FAS	All enrolled patients who received at least one administration (full or partial dose) of study drug. Patients will be grouped according to the treatment assignment as described in Section 5.1.1 Treatment/Patient Group Terminology by Cohort.
	Safety-evaluable	All patients enrolled in the OLE study who received at least one administration (full or partial dose) of zinpentraxin alfa. Patients will be grouped according to the treatment assignment as described in Section 5.1.1 Treatment/Patient Group Terminology by Cohort.
	PRO-evaluable	All enrolled patients who received at least one administration (full or partial dose) of study drug and have an OLE baseline and at least 1 post-baseline assessment.
	HRCT-evaluable	All enrolled patients who received at least one administration (full or partial dose) of study drug and have an OLE baseline and at least 1 post-baseline assessment.
	PK-evaluable	All enrolled patients who received at least one administration (full or partial dose) of study drug and have at least one evaluable post-dose PK sample that is above the lower limit of quantification and with sufficient data to determine plasma concentrations of zinpentraxin alfa at specified timepoints, unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred which may interfere with PK evaluation.
Cohort A, B, C	Survival population	All patients that entered the study

FAS = full analysis set; HRCT = high-resolution computed tomography; PRO = patient-reported outcomes; PK=pharmacokinetic.

5. STATISTICAL ANALYSES

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

The following sections are applicable to Cohorts A and B of the study. Patients initially allocated to Cohort C will be used for survival follow-up only without any safety or efficacy assessments.

5.1 GENERAL CONSIDERATIONS

All analyses will be reported separated by cohort.

Patients who are rolling-over from Study WA42293 will not be required to repeat safety and efficacy assessment at Day 1 if the visit occurs within 4 weeks of Week 52: in these cases, assessments from Week 52 of Study WA42293 will be used as Day 1 assessments.

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

All efficacy analyses will be performed on the full analysis set (FAS) population, unless otherwise specified. Patients in Cohort B will be analyzed according to the treatment assigned at randomization by interactive voice/Web-based response system (IxRS) in the parent study.

Cohort B collected data will not be analyzed before unblinding of the code of the treatment received by the patient during the parent Study WA42293. The main analysis will take place at the time of unblinding and main analysis of the parent Study WA42293. If unblinding of the Study WA42293 will occur earlier than the 52-week visit of the last patient enrolled in Cohort B, additional efficacy analysis will be implemented at the time when all patients in Cohort B had their 52-week visit or withdrew from the study, whichever is earlier.

Additional safety update analyses maybe conducted as required by Health Authorities. The final analysis will take place after the last patient last visit (LPLV).

All outputs relevant to Cohort C will have a footnote specifying that most part of the patients has contributed also to Cohort A and Cohort B.

5.1.1 Treatment/Patient Group Terminology by Cohort

The terminology of treatment/patient groups for each cohort under each analysis population is defined below:

Cohort A

- zinpentraxin alfa: all data for all patients

Cohort B

- Placebo: all data for patients as assigned to placebo during analysis in the parent study (actual or planned, depending on the type of the analysis)

- Zinpentraxin alfa: all data for patients as assigned to zinpentraxin alfa during analysis in the parent study (actual or planned, depending on the type of the analysis)
- All patients

Survival population for Cohort C

- From Cohort A: survival data from patients that discontinued or died from Cohort A
- From Cohort B: survival data from patients that discontinued or died from Cohort B for the following treatments
  - Placebo: survival data for patients as assigned to placebo during analysis in the parent study (planned treatment)
  - Zinpentraxin alfa: survival data for patients as assigned to zinpentraxin alfa during analysis in the parent study (planned treatment)
  - All patients
- Directly from Study WA42293: survival data from patients that have discontinued from study treatment or have completed Study WA42293 and have not wanted to receive open-label zinpentraxin alfa.
  - Placebo: survival data for patients as assigned to placebo during analysis in the parent study (planned treatment)
  - Zinpentraxin alfa: survival data for patients as assigned to inpentraxin alfa during analysis in the parent study (planned treatment)
  - All patients

5.2 PATIENT DISPOSITION

The number of patients recruited in OLE study will be tabulated for each cohort (A, B, and C) by region, country, study site, and treatment arm. The FAS, safety-evaluable, HRCT-evaluable, pharmacokinetic (PK)-evaluable, pharmacodynamics (PD)-evaluable, PRO-evaluable populations, and survival population, including numbers of patients in each population will be summarized by cohort as applicable. Patient disposition (the number of patients treated and are ongoing at the end of study reporting period) will be tabulated by Cohorts A and B and the treatment arm. Premature treatment discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized for Cohorts A and B.

5.3 SAFETY ANALYSIS

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

- Incidence and severity of AEs, with severity determined according to the 5-point severity scale (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI CTCAE, v.5.0])

- Incidence and severity of IRRs and other AEs of special interest (AESIs)
- Proportion of patients permanently discontinuing study treatment due to AEs
- Change from baseline in targeted clinical laboratory test results

Safety analyses will be based on patients from safety populations and grouped according to cohorts and the treatment groups described in Section 5.1.1.

Safety will be assessed through descriptive summary of exposure to study drug, seriousness and severity of AEs, and 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, from the start of OLE period till the time of the snapshot or end of the study.

5.3.1 Extent of Exposure

Extent of exposure to study drug during OLE, 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 of OLE phase till the date of the last treatment administration + 4 weeks or the date of the snapshot, whichever occurs first
- Study Duration (Weeks), measured from date of first administration at Baseline Day 1 of OLE phase till the date of the last safety assessment or the date of the snapshot, whichever occurs first
- 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

Exposure to concurrent use of pirfenidone and/or nintedanib will also be summarized descriptively by cohort and treatment group as defined in Section 5.1.1.

5.3.2 Adverse Events

All verbatim (“investigator-reported”) AE terms will be assigned a standardized term (the “Preferred Term [PT]”) and a superclass term using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 scale. A by-patient AE data listing including onset study day, duration, PT, treatment, severity, relationship to treatment, treatment for AE, action taken, and outcome will be provided.

All AEs, 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 [TEAEs]) will be summarized by PT 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 in the OLE study). 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 (SAE occurring in Cohorts A, B, and C before or after the AE reporting period, as described in Protocol Section 5.4 and Protocol Section 5.7).

Number of patients with AE, number of AEs, cumulative incidence of AE as well as the AE rate per 100 patient-years exposure (defined as the number of events/total duration in the study multiplied by 100) will be calculated, along with the corresponding 95% confidence intervals (CIs) for the patient-years' rates of the SOC (exact based on the Chi-square distribution [Ulm 1990]).

Summary tables of the following will be provided for each cohort and the treatment groups as described in Section 5.1.1, including, but not limited to:

- AEs and SAEs of any grade
- AEs by highest NCI CTCAE grade
- Severe AEs (NCI CTCAE 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 defined as follows:
  - 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 Protocol Section 5.4.)
  - Suspected transmission of an infectious agent by the study drug, as defined in Protocol Section 5.3.
  - Suspected IRR with NCI CTCAE Grade ≥ 2
  - Suspected anaphylactic or hypersensitivity reactions (all grades)
  - Acute or suspected exacerbation of IPF (all grades)

- Common AEs, i.e., those occurring in at least 5% of patients
- Suspected IRR (all grades)

Summaries of safety data by baseline concurrent anti-fibrotic therapy will be provided as appropriate.

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

Summaries of confirmed or suspected Coronavirus Disease 2019 (COVID-19) AEs and AEs associated with COVID-19 will also be provided.

A listing of all pregnancies will be presented.

5.3.3 Adjudicated Anaphylactic and Hypersensitivity Reactions

Anaphylaxis and hypersensitivity events as adjudicated positively by the anaphylaxis adjudication committee will be summarized descriptively. Listing of TEAEs of anaphylaxis and hypersensitivity and their assessment by an Independent Anaphylaxis Adjudication Committee as per the Anaphylaxis Adjudication Committee Charter will be produced by cohort.

5.3.4 Laboratory Data

Descriptive summaries of laboratory values at baseline (defined as the last assessment before or on Day 1 of OLE study), by visit, and change from baseline throughout the study will be tabulated by cohort and each treatment arm as defined in Section 5.1.1. Highest NCI CTCAE grade post-baseline will also be reported and shift tables from baseline to worst value during the study post-baseline will be presented by cohort and treatment arm as defined in Section 5.1.1.

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 (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], estimated glomerular filtration rate) 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 cohort and 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.

5.3.5 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 cohort and treatment group as defined in Section 5.1.1. Baseline is defined as the last assessment prior to treatment on Day 1 of OLE study.

5.3.6 ECGs

A shift table for patients with ECGs clinically significant abnormalities (from baseline to worst condition after baseline) will be produced.

5.3.7 Other Safety Endpoints

Summaries of safety data by ADA status will be provided as appropriate. See Section 5.6.5 for more details on ADA status.

5.4 EFFICACY ANALYSIS

All efficacy analyses will be performed on the FAS population for cohort A and B, unless otherwise specified. Efficacy analysis will be presented over time by cohort and treatment group as defined in Section 5.1.1.

Efficacy will be assessed by annual rate of change in FVC (mL), 6MWD, FVC% predicted, and carbon monoxide diffusing capacity (DL_{CO}), time to disease progression, and survival as measured by all-cause mortality, IPF-related mortality and respiratory-related mortality.

All efficacy parameters will be summarized descriptively, and as all patients will be receiving zinpentraxin alfa, there will be no hypothesis testing between treatment groups defined for cohort B. Wherever possible 95% confidence intervals will be reported for estimates.

The annual rate of change in FVC (mL), 6MWD, FVC% predicted, and DL_{CO} will be calculated using the slope from a linear mixed effect model with random intercept

(subject) and random slope (time), using measurements collected at each time point in this study. The model will include patient gender, age, and height at baseline, study day of the visit and strata (region and concurrent use of IPF treatment). When analyzing data from Cohort B, treatment group and treatment by time interaction will be added to the model as covariates.

With respect to handling of missing data in the assessment of spirometry data (FVC [mL], FVC% predicted, and DL_{CO}), all measurements that meet the minimal level of quality (except those recorded after lung transplantation) will be used. For the purpose of determining the annual rate of change estimates, a hypothetical strategy will be utilized where values will be implicitly imputed from the model for the majority of data impacted by intercurrent events with the exception of death due to IPF.

For death, a hypothetical strategy will be utilized where after death assessments will be implicitly imputed using linear mixed-effect model. See Table 3 for details.

Table 3 Analysis Strategy for Intercurrent Events for FVC, 6MWD, FVC% Predicted, and DL_{CO}

Intercurrent Event (ICE)		Analysis Strategy
Any change to treatment	Permanent study drug discontinuation	Hypothetical strategy Implicit imputation using linear mixed-effect model
Any change in standard of care (SOC), with pirfenidone or nintedanib therapy	SOC started during study Change in dose of SOC SOC discontinued SOC switch (from pirfenidone to nintedanib or vice-versa)	Treatment policy All measurements post ICE analyzed
Other concomitant treatment	Use of prohibited concurrent medication (Protocol Section 4.4.2)	Treatment Policy All measurements post ICE analyzed
Terminal events	Death	Hypothetical strategy Assessments following death will be implicitly imputed using linear mixed-effect model
	Lung transplantation	Hypothetical strategy Measurements collected after lung transplantation excluded from the analysis Implicit imputation using linear mixed-effect model
	Hospitalization for COVID-19	Treatment Policy strategy All measurements post ICE analyzed

COVID-19=Coronavirus Disease 2019; ICE = intercurrent event; SOC = standard of care.

In the hypothetical strategy, the model implicitly imputes missing data based on an individual's estimated rate of worsening of lung function prior to study discontinuation (i.e., assuming missing at random).

In addition, summaries using all observed data will be performed.

Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) on absolute values and their change from baseline for several observed efficacy evaluations (FVC [mL], 6MWD, FVC% predicted, and DL_{CO}) will be presented over time by cohort and treatment group as defined in Section 5.1.1. Baseline is defined as any last assessment prior to treatment on Day 1 of OLE study.

5.4.1 Time-to-Event 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
- Survival, as measured by all-cause mortality, IPF-related mortality and respiratory-related mortality

Descriptive statistics for the frequency of each type of event will be provided. The Kaplan-Meier plot, median time to event, and their 95% CIs.

Time-to-event will be measured in reference to Baseline Day 1 of OLE study through the end of study or the time of the data-cut, whichever occurs first. For time to disease progression and survival (as measured by all-cause mortality, IPF-related mortality and respiratory-related mortality), patients without an event will be censored at the last clinic assessment.

The strategy for the time-to-event endpoints is summarized below in Table 4.

Table 4 Strategy for Addressing Intercurrent Events: Time-to-Event Endpoints

Endpoint	Intercurrent Events and Strategy
Time to disease progression, defined as time to first occurrence of ≥10% absolute decline in % predicted FVC, ≥15% relative decline in 6MWD, or death	Any patients who undergo lung transplantation will be censored at the date of the transplant (hypothetical strategy) Any patients who withdraw from treatment will be censored at the date of last disease progression assessment, i.e., % predicted FVC and 6MWD (hypothetical strategy)
Survival, as measured by all-cause mortality, IPF-related mortality and respiratory-related mortality	Any patients who undergo lung transplantation will be censored at the date of the transplantation (hypothetical strategy) Any patients who withdraw from treatment will be censored at the date of withdrawal (hypothetical strategy)

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

5.5 EXPLORATORY EFFICACY ANALYSIS

Some exploratory efficacy analyses will be performed on the FAS population, if not otherwise specified. Patients in Cohort B will be analyzed according to the treatment as it was assigned during efficacy analysis of the parent study. Analysis will be presented over time by cohort and treatment group as defined in Section 5.1.1. Baseline is defined as the last assessment prior to treatment on Day 1 of OLE study.

No intercurrent event will be considered in the exploratory endpoint analysis (with the exception of the time to event exploratory endpoints) and no imputation of the missing data is forecasted.

Patient-Reported Outcomes (PRO)

Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) on observed values and their change from baseline for patient-reported outcomes (PRO) efficacy endpoints (UCSD-SOBQ, SGRQ [individual domains and total score], and EuroQol 5-Dimension, 5-Level Questionnaire [EQ-5D-5L] index-based, and visual analog scale scores) will be presented for the PRO analysis population over time by cohort and treatment group as defined in Section 5.1.1.

Change-from-Baseline Exploratory Endpoints: HRCT

In Cohort B patients, summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) on the raw values at each visit and the change from baseline to each visit through Week 52 and Week 104 will be computed for the quantitative HRCT imaging analysis parameters by treatment group as defined in Section 5.1.1 for Cohort B.

Acute Exacerbation of IPF Endpoints

Summary statistics for continuous variables will be prepared by cohort and treatment group (as defined in Section 5.1.1) for the total number and rate (per year) of acute or suspected exacerbations during the OLE period.

The number and proportion of patients with at least one acute or suspected exacerbation during the OLE period, as determined by Adjudication Committee, will be tabulated by cohort and treatment group as defined in Section 5.1.1.

Healthcare Utilization Exploratory Endpoints

Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) on absolute values 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.

Statistics will be presented over time by cohort and treatment group as defined in Section 5.1.1.

5.5.1 Time-to-Event Exploratory Endpoints

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

- 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 Adjudication Committee)
- Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF, as determined by Adjudication Committee

Time-to-event will be measured in reference to baseline Day 1 of OLE study through the end of study or the time of the data-cut, whichever occurs first. 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 known alive day.

The strategy for the time-to-event endpoints is summarized below in Table 5.

Table 5 Strategy for Addressing Intercurrent Events: Time-to-Event Exploratory Endpoints

Endpoint	Intercurrent Events and 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 Adjudication Committee)	Deaths due to IPF or other respiratory causes will be treated as disease progression and counted as event of interest (composite strategy) Deaths due to other causes will be censored Any patients who undergo lung transplantation will be censored at the date of the transplantation (hypothetical strategy) Any patients who withdraw from treatment will be censored at the date of withdrawal (hypothetical strategy)
Time to first acute exacerbation of IPF, or suspected acute exacerbation of IPF, as determined by Adjudication Committee	Deaths due to IPF will be treated as disease progression and counted as event of interest (composite strategy) Deaths due to non-IPF causes will be censored Any patients who undergo lung transplantation will be censored at the date of the transplantation (hypothetical strategy) Any patient who withdraws from treatment will be censored at the date of withdrawal (hypothetical strategy)

IPF = idiopathic pulmonary fibrosis.

5.5.2 Additional Exploratory Efficacy Endpoints

Exploratory analyses may also be performed for additional measures (see below the list of additional exploratory efficacy endpoints) and subgroups of interest including concurrent use of IPF treatment and geographic region (see Section 5.6.6 for the complete list).

The additional exploratory efficacy endpoints are:

- Change from baseline in FVC% predicted, FVC (mL), by concurrent therapy stratum (i.e., with nintedanib treatment vs. with pirfenidone treatment vs. without pirfenidone or nintedanib treatment)
- Change from baseline in FVC% predicted, FVC (mL), by MUC5B status
- Change from baseline in 6MWD (m), by concurrent therapy stratum (i.e., with nintedanib treatment vs. with pirfenidone treatment vs. without pirfenidone or nintedanib treatment)

Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) on absolute values and their change from baseline.

5.6 OTHER ANALYSES

5.6.1 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.

5.6.2 Summaries of Demographics and Baseline Characteristics

Unless otherwise specified, the baseline value for each variable will be considered for the assessment collected on baseline Day 1, prior to administration of first study drug during OLE period. For subjects in Cohort C directly recruited from Study WA42293, baseline will be Day 1, prior to administration of first study drug during double-blind period.

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 cohort and treatment group (as defined in Section 5.1.1) 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.

5.6.3 Pharmacokinetic Analyses

The pharmacokinetic (PK)-evaluable population will consist of patients from Cohort A and Cohort B with sufficient data to determine plasma concentrations of zinpentraxin alfa at specified timepoints, unless major protocol deviations or unavailability of information (e.g., exact blood sampling time) occurred which may interfere with PK evaluation, with patients grouped according to treatment received.

Individual and mean plasma zinpentraxin alfa concentration versus time data will be listed and summarized (mean, standard deviation, coefficient of variation mean,

geometric mean, coefficient of variation geometric mean, median, minimum, and maximum).

The PK parameters for zinpentraxin alfa in plasma will be estimated as appropriate for each subject profile 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.

5.6.4 Biomarker Analyses

Biomarkers will be assessed at baseline and subsequent timepoints following administration of zinpentraxin alfa (both Cohort A and Cohort B). Biomarkers will be

presented as absolute value over time and/or percent change relative to baseline over time. Biomarker levels at baseline or over time may be compared with efficacy or safety measurements to assess prognostic or predictive properties.

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

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.

5.6.5 Immunogenicity Analyses

The following summaries will be provided for both Cohort A and Cohort B (only for patients who enrolled into the Study WA42293 prior to 1 June 2022) by the treatment group as defined in Section 5.1.1:

- Numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence)
- Number and percent of patients with at least one treatment-induced ADA
- 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 pharmacokinetics may be analyzed and reported via descriptive statistics.

5.6.6 Analyses of Subgroups of Interest

The generalizability of efficacy endpoint results will be investigated by estimating the longitudinal treatment effect in subgroups based on stratification factors used in the parent study 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 cohort and treatment group as defined in Section 5.1.1. Summaries of some selected endpoints by these subgroups will be provided in forest plots.

Safety and immunogenicity analyses will be performed separately for first and second generation of zinpentraxin alfa.

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
Generation drug product	First generation of zinpentraxin alfa Second generation of zinpentraxin alfa

5.6.7 Analyses of China Subpopulation

If applicable, a separate analysis will be performed for the China subpopulation.

The analysis population for the China subpopulation analyses includes all patients enrolled during WA42293 study at sites in mainland China, Hong Kong, and Taiwan. Data for the China subpopulation will be analyzed using the same statistical methods as described in Sections 5.1– 5.5 when data allow.

5.6.8 Other Analyses

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology will be summarized descriptively by time point and treatment group.

6. SUPPORTING DOCUMENTATION

Refer to Appendix 1 below for details.

Appendix 1 Changes to Protocol-Planned Analyses

The objective “To assess the long-term impact of 10 mg/kg zinpentraxin alfa plus SOC on healthcare utilization for respiratory events” with the respective endpoints are added in Table 1 even if not reported in the objective section of the protocol. Analysis are described in Section 5.5 at the “Healthcare Utilization Exploratory Endpoints” subsection.

7. REFERENCES

Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med 2016;194:265–75.

FDA Guidance for Industry 2006. US Food and Drug Administration. Guidance for clinical trial sponsors: establishment and operation of clinical trial data monitoring [resource on the internet]. 2006 [cited: 12 March 2020].

Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol 1990;131:373−5.

Signature Page for Statistical Analysis Plan WA42294 Version 1-Zinpentraxin Alfa
System identifier: RIM-CLIN-449204

Approval Task	[redacted] Company Signatory 24-Aug-2022 18:25:57 GMT+0000