STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 2b Randomized, Double-blind, Placebo-controlled, Repeat-dose, Multicenter Trial to Evaluate the Efficacy, Safety, and Tolerability of HZN-825 in Subjects with Idiopathic Pulmonary Fibrosis
Name of Test Drug:	HZN-825
Protocol Number:	HZNP-HZN-825-303
Protocol Version (Date):	4.0 (01 December 2022)
Analysis Type:	Interim and Final Analysis
Analysis Plan Version:	2.0
Analysis Plan Date:	16 August 2024
Analysis Plan Author:	▮▮▮▮▮

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LIST OF ABBREVIATIONS

6MWT	6-Minute Walk Test
AEs	adverse events
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATS	American Thoracic Society
BID	two a day
BMI	body mass index
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CS	clinically significant
CSH	hererogenous compound syummetry
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DLCO	diffusing capacity of the lungs for carbon monoxide
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FCS	fully conditional specification
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
HLGT	high-level group term
HRCT	high resolution computed tomography
hsCRP	high sensitivity C-reactive Protein
ICE	intercurrent events
ID	identification
IDMC	independent data monitoring committee
IPF	idiopathic pulmonary fibrosis
IPF-RAE	IPF-related acute exacerbation
IRT	interactive response technology
ITT	intention-to-treat
K-BILD	King's Brief Interstital Lung Disease
LCQ	Leicester Cough Questionnaire
L-IPF	Living with IPF Questionnaire

LLT	lower-level term
LPAR1	Lysophosphatidic Acid Receptor 1
LS	least squares
MAR	missing at random
MCS	mental component score
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MNAR	missing not at random
msec	millisecond
n	number of subjects
NCS	not clinically signfican
PCS	physical component score
PD	protocol deviation
PFS	progression-free survival
PK	pharmacokinetics
PMM	pattern mixture model
PT	preferred term
PYE	patient years of exposure
Q1	first quartile
Q3	third quartile
QD	one a day
RCTC	Rheumatology Common Toxicity Criteria
SAEs	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMQ	standard MedDRA query
SOC	system organ class
SpO2	supplemental oxygen
SRT	safety review team
SSc	systemic sclerosis
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures
TOEP	Toeplitz
TOEPH	heterogeneous Toeplitz
TOR	titrated oxygen requirement
ULN	upper limit of normal
WHO	World Health Organization

1.   INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, listings, and figures (TLFs) in the clinical study report (CSR) for Trial HZNP-HZN-825-303. This SAP is based on the trial protocol Version 4.0 dated 01 December 2022.

1.1.   Trial Objectives

The trial will be conducted in 2 parts, Part 1 (Core Phase) followed by Part 2 (Extension Phase). The Core Phase will include a 52-week, randomized, double-blind, placebo-controlled treatment period and the Extension Phase will include a 52-week, open-label extension (OLE).

1.1.1.   Part 1 (Core Phase)

1.1.1.1.   Primary Objective

The primary objective of the Core Phase is to demonstrate the efficacy of 2 dose regimens of HZN-825 versus placebo in subjects with Idiopathic Pulmonary Fibrosis (IPF), as determined by a comparison of change in forced vital capacity (FVC)% predicted after 52 weeks of treatment.

1.1.1.2.   Secondary Objectives

1. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the proportion of subjects with decline in FVC % predicted ≥ 10% from Baseline after 52 weeks of treatment (key secondary objective).

2. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the changes from Baseline in the 6-Minute Walk Test (6MWT) after 52 weeks of treatment.

3. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) after 52 weeks of treatment.

4. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the Living with IPF (L-IPF) after 52 weeks of treatment.

5. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the Leicester Cough Questionnaire (LCQ) after 52 weeks of treatment.

6. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the rate of hospitalization due to respiratory distress up to 52 weeks of treatment.

7. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the composite endpoint of progression-free survival (PFS) where progression includes decline in FVC % predicted ≥ 10% from Baseline or death over 52 weeks of treatment.

8. Assess safety and tolerability of HZN-825 inclusive of, but not limited to adverse events (AEs), serious adverse events (SAEs) and adverse event of special interest (AESI).

9. Evaluate the pharmacokinetics (PK) of HZN-825.

1.1.1.3.   Exploratory Objectives

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6. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on mortality due to respiratory deterioration up to 52 weeks of treatment.

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1.1.2.   Part 2 (Extension Phase)

The overall objective of the Extension Phase is to investigate the long-term efficacy, safety and tolerability of HZN-825, a selective antagonist of LPAR1, administered at a dose of 300 mg BID to subjects with IPF in a 52-week OLE following completion of the Core Phase of the trial. The dose for the Extension Phase may be modified based on the results of the Core Phase.
Two types of Baseline are defined for the Extension Phase:

• OLE Baseline, defined as the latest measurement prior to the first dose of HZN-825 in Extension Phase

• HZN-825 Baseline, defined as the latest measurement prior to the first dose of study drug (either HZN-825 or Placebo) in the Core Phase

1.1.2.1.   Primary Objective

The primary efficacy objective is to assess the efficacy of HZN-825 in subjects with IPF after 52 weeks of open-label treatment.

1.1.2.2.   Safety Objective

The safety objective is to examine the safety and tolerability of 52 weeks of open-label treatment with HZN-825 based on:
• TEAE assessment

• Concomitant medication use

• Vital signs

• 12-lead electrocardiogram (ECG)

• Clinical safety laboratory results

The primary safety objective is to examine the TEAEs during 52 weeks of open-label treatment with HZN-825.

1.1.2.3.   Exploratory Objectives

The exploratory efficacy objective is to evaluate the efficacy of 52 weeks of open-label treatment with HZN-825 via additional efficacy measurements:
• Proportion of subjects with decline in FVC % predicted ≥10%

- 6MWT

- K-BILD

- L-IPF

- LCQ

- ███████

- Hospitalization due to respiratory distress

- Composite endpoint of PFS, where progression includes decline in FVC % predicted ≥10% or death

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The exploratory PK objective is to evaluate the PK of HZN-825.

1.2.   Trial Design

1.2.1.   Overall Trial Design and Plan

The trial will be conducted at approximately 100 trial sites in North America, Europe, South America, Africa, Asia (including Japan) and Australia. The trial comprises 2 parts. Part 1 (Core Phase) is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter trial to evaluate the efficacy, safety and tolerability of HZN-825 in subjects with IPF. Part 2 (Extension Phase) is an optional, open-label, repeat-dose, multicenter extension of the Core Phase.

1.2.2.   Design of the Core Phase of the Trial

This is a randomized, double-blind, placebo-controlled, repeat-dose, international multicenter trial to evaluate the efficacy, safety, and tolerability of HZN-825 in subjects with IPF. Approximately 135 subjects who meet the trial eligibility criteria will be randomly assigned by central randomization in a 1:1:1 ratio on Day 1 to receive HZN-825 300 mg QD, HZN-825 300 mg BID, or placebo for 52 weeks using the following 2 stratification factors:

1. Concomitant use of approved IPF therapy (i.e., nintedanib or pirfenidone): yes or no

2. FVC % predicted at Baseline: ≥ 70% or < 70%

The Core Phase will include up to an 8-week Screening Period and a 52-week Double-blind Treatment Period. Subjects will take their first dose of trial drug at the clinic on Day 1 (Week 0) and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. Subjects who complete the 52-week Double-blind Treatment Period may be eligible to enroll into an Extension Phase of the trial. If the subject does not enroll into the Extension Phase, a Safety Follow-up Visit will occur 4 weeks after the last dose of trial drug.

If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 52. If a subject prematurely discontinues trial drug and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 52 assessments.

An interim analysis with a futility analysis will be performed when ████████████ ██ ████████████████ These unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC) and will be used to inform the conduct of the current trial. The IDMC will include at least 1 statistician and at least 2 clinicians experienced in clinical trials and managing IPF subjects. The IDMC charter will include processes to unblind select Horizon personnel who are not directly involved with the trial conduct to assess unforeseen issues.
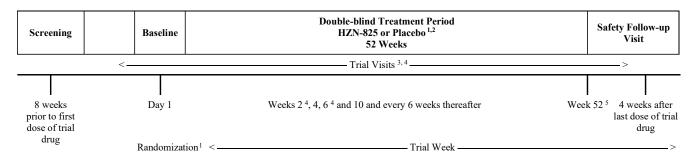
At the interim analysis, the IDMC will provide recommendation to select Horizon personnel not involved in the oversight of the trial to facilitate trial continuation and dose selection for future trials. To support decisions on future dose selection and future trial design, a Horizon unblinded team may be established and receive unblinded data and perform ad hoc analyses, as needed. All unblinded data and analysis results made available to the Horizon unblinded team will be archived to allow for any potential post hoc assessments of bias. For additional details, please refer to the IDMC charter and Blinding Maintenance Plan for this trial.

An overview of the Core Phase trial design is presented in Figure 1.

Figure 1. Schematic of Trial Design – Core Phase

Screening		Baseline	Double-blind Treatment Period HZN-825 or Placebo [1,2] 52 Weeks	Safety Follow-up Visit
			< ———————————— Trial Visits [3, 4] ———————————— >	
8 weeks prior to first dose of trial drug		Day 1	Weeks 2 [4], 4, 6 [4] and 10 and every 6 weeks thereafter	Week 52 [5] 4 weeks after last dose of trial drug
	Randomization [1] < ———————————— Trial Week ———————————— >			

BID=twice daily; QD=once daily

1. Subjects will be randomized in a 1:1:1 ratio to receive HZN-825 300 mg QD, HZN-825 300 mg BID or placebo.
2. If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 52. If a subject prematurely discontinues trial drug and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 52 assessments. Subjects not entering the 52-week Extension Phase will return to the clinic 4 weeks after the last dose of trial drug for a Safety Follow-up Visit.
3. Visit windows are ±3 days for Week 4, ±7 days for Week 10 to Week 52, inclusive, and ±14 days for the Safety Follow-up Visit.
4. Visits at Weeks 2 and 6 are remote (telephone) visits with a ±3-day window.
5. Subjects who complete the Double-blind Treatment Period (Week 52) may be eligible to enter a 52-week Extension Phase of the trial.

1.2.3.   Design of the Extension Phase of the Trial
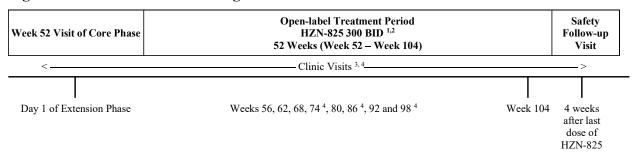
The Extension Phase of the trial is an optional, open-label, repeat-dose, multicenter extension of the Core Phase. Subjects who complete the Double-blind Treatment Period (Week 52) in the Core Phase of the trial may be eligible to enter this 52-week Extension Phase. Subjects entering the Extension Phase will complete the Week 52 Visit, which will be considered Day 1 of the Extension Phase and will receive their first dose of open-label HZN-825 in the Extension Phase at the clinic and return to the clinic for trial visits at Weeks 56, 62 and 68, then every 12 weeks through Week 104. The Week 52 Visit activities will serve as Baseline for the Extension Phase. Subjects will return to the clinic for a Safety Follow-up Visit 4 weeks after the last dose of HZN-825.

If a subject prematurely discontinues HZN-825, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 104. If a subject prematurely discontinues HZN-825 and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 104 assessments.
An overview of the Core Phase trial design is presented in Figure 2.

Figure 2. Schematic of Trial Design – Extension Phase

Week 52 Visit of Core Phase	Open-label Treatment Period HZN-825 300 BID [1,2] 52 Weeks (Week 52 – Week 104)	Safety Follow-up Visit

< ——————————————— Clinic Visits [3, 4] ——————————————— >

| Day 1 of Extension Phase | Weeks 56, 62, 68, 74 [4], 80, 86 [4], 92 and 98 [4] | Week 104 | 4 weeks after last dose of HZN-825 |

BID=twice daily
1. The HZN-825 dose may be modified based on the results of the Core Phase.
2. If a subject prematurely discontinues open-label HZN-825, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 104. If a subject prematurely discontinues open-label HZN-825 and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 104 assessments.
3. Visit windows are ±5 days for Week 56, ±7 days for Week 62 to Week 104, inclusive, and ±14 days for the Safety Follow-up Visit.
4. Visits at Weeks 74, 86 and 98 are remote (telephone) visits with a ±7-day window.

1.3.　　　　　　Sample Size and Power

Approximately 135 subjects (45 subjects per treatment group) will be enrolled in the trial. Based on a prior trial of pirfenidone [Nathan et al., 2019] in a similar subject population, change in FVC % predicted is expected to have a standard deviation of 6% to 9% after 52 weeks of treatment. Assuming a clinically important difference between HZN-825 and placebo is 3% and a common standard deviation is 9%, a sample size of 45 subjects per treatment group in the Core Phase will provide 85% probability to detect a positive signal (FVC % predicted difference for each dose vs. placebo at Week 52 >1%) and 70% probability to detect a positive signal (FVC % predicted difference for each dose vs. placebo at Week 52 >2%). If the true FVC % predicted difference for each dose versus placebo at Week 52 is 0%, then there is only 15% probability to detect a positive signal (FVC % predicted difference for each dose vs. placebo at Week 52 >2%).

The sample size for the Extension Phase is based on the number of subjects who complete the Core Phase.
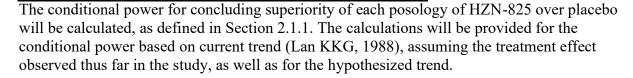
2.   TYPE OF PLANNED ANALYSIS

2.1.   Interim Analysis

An external multidisciplinary IDMC will review the progress of the trial and perform interim reviews of the study data in order to protect subject welfare and preserve trial integrity. The IDMC will include at least 1 statistician and at least 2 clinicians experienced in clinical trials and the therapeutic area. IDMC review will be conducted according to the timelines outlined in the IDMC charter.
A futility analysis for dose selection will be conducted at the interim analysis ▮▮▮▮▮
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The conditional power for concluding superiority of each posology of HZN-825 over placebo will be calculated, as defined in Section 2.1.1. The calculations will be provided for the conditional power based on current trend (Lan KKG, 1988), assuming the treatment effect observed thus far in the study, as well as for the hypothesized trend.

The IDMC will recommend stopping the study for a conclusion of futility if the conditional power for both doses is less than 10% The IDMC may recommend stopping only one posology only if there is a clear safety signal that precludes continuation of one posology. Unless this occurs, the IDMC will either recommend continuing both posologies or stopping both posologies in this study.

If the IDMC recommends continuing the study, the IDMC will further recommend which of the two posologies will be used for investigation in future trials of HZN-825. The IDMC members will use the following decision criteria in making this recommendation:

1   If one of the two posologies has a clear safety signal that precludes further study, the other posology will be recommended.

2   If only one of the two posologies has a conditional power of at least 10% without additional safety signals then that posology will be recommended.

3   Similarly, if one of the two posologies has a conditional power that exceeds that of the other posology by at least 10 percentage points, without additional safety signals, the posology with the higher conditional power will be recommended.

4   If both posologies have similar conditional power and no unique safety signals appear with either posology, the IDMC is expected to recommend the lower dose.

To support the dose selection, and as part of the Week 28 unblinded interim analysis the FVC % predicted change from Baseline at Week 28 may be evaluated in full analysis set (FAS) subjects with concomitant treatment of standard of care at the baseline. The positive signal in the FVC % predicted change from Baseline at Week 28 and related results in subjects with standard of care will support the dose selection and future trial design.

An executive representative from Horizon will receive the recommendation from the IDMC chair. This Horizon executive representative is a senior management representative who does not have day to day responsibilities in the study and who does not have direct communication with study site personnel or study subjects.

The IDMC chair will present any data necessary to support the decision, including necessary unblinded data. All unblinded data presented to the Horizon representative will be archived to demonstrate the amount of unblinded data presented to the Horizon for post hoc assessments of bias.

A Horizon unblinded team will be established at the interim analysis. This team will receive unblinded data and perform ad hoc analyses to support decisions on dose selection, future trial design, and preparation for the potential meeting and/or requests from regulatory authorities. This team may include clinical, biostatistical, regulatory and other function representatives as needed. The unblinded information will be restricted from Horizon trial team members who are involved in any aspect of trial conduct and management. The unblinded team members will not participate in remaining trial conduct until the final unblinding of the trial has occurred following the Core Phase completion. All unblinded data and analyses results made available to the unblinded team will be archived to enable for a potential post hoc assessments of bias. Additional details of the procedural handling of the interim analysis are described in the Blinding Maintenance Plan.

The IDMC's role and responsibilities and the scope of analysis to be provided to the IDMC are provided in a mutually agreed upon charter, which defines the IDMC membership, meeting logistics, and meeting frequency.

2.1.1.   Calculation of Conditional Power

At the interim, the conditional power for the current trend and the hypothesized trend will be calculated (Lan KKG, 1988). The conditional power will be presented for the comparison of each dose regimen to the placebo.

Then Conditional Power at time t is given by:

$$\text{Conditional Power} = \Phi[Z_{CP}],$$

where Φ is the standard normal cumulative distribution function and

Current Trend: $Z_{CP}(t) = \dfrac{\frac{Z_t}{\sqrt{t}} - Z_{\alpha/2}}{\sqrt{1-t}}$ at t=0.5 and $\alpha = 0.10$

Hypothesized (H1) trend: $Z_{CP}(t) = \dfrac{\left(Z_t * \sqrt{t}\right) + (1-t)*\left(Z_{\alpha/2} + Z_\beta\right) - Z_{\alpha/2}}{\sqrt{1-t}}$

at t=0.5 and $\alpha = 0.10$, $\beta = 0.150$

The statistic Z_t will be calculated as Z_t = (LS Mean Difference)/Standard Error, with these values obtained from the SAS statistical output.

2.2.   Safety Analysis for Safety Review Team (SRT) Meetings

Safety and tolerability monitoring are planned at the following trial milestones:

- After 50 new subjects are treated through Week 4 until all subjects in the trial (~135) have been treated through week 4, which will be 1st through 3rd SRT meeting or approximately quarterly, whichever comes first

- Approximately quarterly after all subjects have been treated through Week 4 through the end of the trial

The results of these analyses will determine if the trial will continue at the current dose levels. Trial blind will not be broken, and all analyses will be done with pooled treatment groups. The content of the outputs for the safety review meetings is described in the study Safety Review Meeting Charter.

2.3.   Primary Analysis

The primary analysis will be conducted after all subjects have completed Core Phase or discontinued prematurely. The analysis includes all data collected at the time of database lock.

2.4.   Final Analysis

The final analysis will be performed after all subjects have completed OLE Phase or discontinued prematurely. Full safety and efficacy data for subjects who entered OLE treatment period will be included.

2.5.   Changes from the Protocol Planned Analyses

The definition of HZN-825 Baseline has been updated from the protocol. This adjustment is essential to facilitate a comprehensive comparison of data over 104 weeks across all cohorts. As a result, HZN-825 Baseline has been redefined as the latest measurement prior to the first dose of study drug (either HZN-825 or Placebo) during the Core Phase.

For efficacy analysis, the prior use of IPF approved therapy will be used as a covariate in the mixed model for repeated measures instead of concomitant use of IPF approved therapy. In earlier protocol versions, the prior use of IPF approved therapy was used as a stratification factor, while concomitant use of IPF approved therapy was restricted. In protocol version 4, concomitant use of IPF approved therapy was permitted and used as a stratification factor. However, only a small number of enrolled subjects were on concomitant IPF therapy. To ensure a robust model estimate, the prior use of IPF approved therapy will be used in the model. Additional subgroup analysis will be conducted as needed, focusing on subjects who were on concomitant use of IPF approved therapy.

3.   GENERAL CONSIDERATIONS FOR DATA ANALYSES

Categorical variables will have the number and percentage of subjects in each category presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

All statistical tests will be 2-sided and performed at the 10% significance level unless otherwise specified.

For additional details on data presentation, refer to the tables, listings, and figures (TLF) document.

3.1.   Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before the trial blind is broken for analysis.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1.   All Subjects Randomized Set

All Subjects Randomized Analysis Set includes all subjects who were randomized in the trial. This analysis set will be used for disposition summaries and will be analyzed by randomized treatment group.

3.1.2.   Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized and took at least 1 dose of study drug. This is the primary analysis set for efficacy analyses for the Core Phase. Subjects will be analyzed by randomized treatment group.

3.1.3.   Safety Analysis Set

The Safety Analysis Set for the Core Phase (SAF) includes all subjects who took any dose of study drug during the Core Phase. This will be the primary analysis set for Core Phase safety analysis. Subjects will be analyzed by actual treatment received.

3.1.4.   OLE Phase Analysis Set

The OLE Phase Analysis Set (OLE-SAF) includes all subjects that are enrolled in OLE Phase and took at least 1 dose of study drug during the OLE Phase. This analysis set will be the

primary analysis set for both efficacy and safety for the OLE Phase and combined periods. Subjects will be analyzed by actual treatment received in Core Phase.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

3.2. Subject Grouping

For analyses based on the FAS Analysis Set, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. Actual treatment will be classified as follows:

- A subject who received only placebo will be classified as a subject in the placebo group.

- A subject who received any active treatment will be classified as a subject in the active treatment group.

- A subject who received different active doses at different dosing visits during the study will be included in the group of the highest active dose that he/she received.

For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

3.3. Examination of Subject Subgroups

Subgroupings based on the baseline characteristics listed below may be explored for analysis of the primary efficacy endpoint and key secondary efficacy endpoint.

The presumed prognostic baseline characteristics include the following:

1. Age (< 65 years and ≥ 65 years)

2. Sex (male and female)

3. Weight (<65 kg and ≥ 65 kg)

4. Race (American Indian or Alaska Native, Asian, Black/African American, Native Hawaiian or Other Pacific Islander, White, or Other)

5. Baseline FVC% predicted ($\geq 70\%$, $<70\%$)

6. Concomitant use of approved IPF therapy (i.e., nintedanib or pirfenidone): yes or no

7.   Prior use of approved IPF therapy (i.e, nintedanib or pirfenidone): yes or no

8.   IPF diagnosis duration (< 3 years, ≥ 3 years)

9.   Region (North America, Europe, South America, Africa, Asia (including Japan) and Australia)

If the actual size of the individual subgroup category is too small (≤10% of treated subjects), then the individual groups will be pooled in a meaningful way. If pooling cannot be done (e.g. if there are only two categories in the subgroup) then the subgroup analysis will not be performed.

3.4.   Multiplicity Adjustment

The overall statistical level is $\alpha=0.10$ (2-sided). Because 2 dose regimens of HZN-825 will be compared to placebo, a hierarchical testing procedure will be used for multiple comparisons. Therefore, $\alpha=0.10$ (2-sided) will be used in the analysis. The hierarchical testing procedure will be used for the primary and key secondary endpoint. For the primary endpoint, the BID dose will be tested versus placebo first; if significant, the QD dose will then be tested. If 1 or 2 dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur. If both HZN-825 doses are statistically significantly better than placebo for primary efficacy endpoint, the testing procedure will continue for the key secondary endpoint and will be similar to that performed for the primary endpoint.

Although p-values will be provided for the other secondary and exploratory endpoints, they will not be used for inferential purposes.

3.5.   Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

The handling of missing or incomplete dates for last dosing date of study drug and AE onset is described in the TLF shells document. Refer to Section 6 for details on how to handle missing data for efficacy analyses.

3.6.   Definition of Baseline

Unless otherwise specified, the baseline value (Baseline) is defined as the last non-missing observation prior to the first dose of study drug. The two types of Baseline for the OLE Phase are defined in section 1.1.2. In cases where baseline measurements are taken on the same day as study drug and no times are reported, it will be assumed that these measurements are taken prior to study drug being administered. In cases where multiple measurements are taken on the same day as study drug without time reported, the average of these measurements will be taken as Baseline. Missing baseline evaluations will not be imputed and will be considered missing.

3.7.   Study Day

Core Phase

The day of the first dose of study drug administration will be considered as study Day 1. Study day will be calculated as:

For postdose study days: assessment date – first dosing date +1

For days prior to the first dose: assessment date – first dosing date

OLE Phase

The day of the first dose of study drug administration in the OLE Phase will be considered as OLE Day 1. OLE Phase study day will be calculated as:

OLE study day: assessment date – OLE first dosing date +1

3.8.   Analysis Windows

For endpoints that present visit-based data, the variables will be summarized based on the scheduled visits with derived analysis visit windows. No visit windows will be derived for the screening period and for PK data. For the visits on and after the 1st dose date, the actual visit date will be mapped to the derived analysis visit windows based on the study day (see Section 3.7).

Visit windows have been constructed so that every observation (unscheduled visits included) collected can be allocated to a specific visit. The actual assessment day will be mapped to the windows defined for each scheduled study visit with following rules:

- If more than 1 assessment falls within a visit window, the closest non-missing valid assessment to the target day will be used in the analysis.
- If 2 non-missing assessment actual dates are equidistant from the target day, the later visit will be used in the analysis.
- For retest values of laboratory and spirometry data, the retest value (the last valid observation assessed on the same visit day or corresponding to the same visit) will be chosen.

The Analysis Visit Window for the primary endpoint FVC % predicted is shown in Table 1. The details for the other analysis visit window rules will be included in the TLF shells document.

Table 1. Analysis Visit Windows for Primary Endpoint

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Core Phase Analysis		
Baseline	Day 1	Day 1/before 1st dose of HZN-825 or Placebo in the Core Phase
Week 4	Day 29	Day 2 to 71
Week 16	Day 113	Day 72 to 155
Week 28	Day 197	Day 156 to 239
Week 40	Day 281	Day 240 to 323
Week 52	Day 365	Day $\geq$ 324 to Core Phase end date
OLE Baseline Analysis		
OLE Baseline	Week 52 Visit Date	OLE Day 1/Before OLE 1st dose
Week 68	OLE Day 113	OLE Day 2 to 155
Week 80	OLE Day 197	OLE Day 156 to 239
Week 92	OLE Day 281	OLE Day 240 to 323
Week 104	OLE Day 365	OLE Day $\geq$ 324
HZN-825 Baseline Analysis		
HZN-825 Baseline	Day 1	Day 1/Before 1st dose of HZN-825 or Placebo in the Core Phase
Week 4	Day 29	Day 2 to 71
Week 16	Day 113	Day 72 to 155
Week 28	Day 197	Day 156 to 239
Week 40	Day 281	Day 240 to 323
Week 52	Day 365	Day 324 to 421
Week 68	Day 477	Day 422 to 519
Week 80	Day 561	Day 520 to 603
Week 92	Day 645	Day 604 to 687
Week 104	Day 729	Day $\geq$ 688

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

The analysis visit windows will also be derived similar to the primary endpoint for other variables, such as laboratory values, vital signs, ECGs, and physical exam findings as needed.

3.9.   Reporting Period

The reporting periods for each phase are defined below. For subjects that entered OLE Phase, both OLE Phase and combined study period will be used in reporting.

Core Phase
Treatment period: time from first dose of study drug intake to 28 days after last dose of study drug intake in the Core Phase.

Study period: time from first dose of study drug intake to the end of Core Phase.

For subjects who entered and took any study drug in OLE Phase, the day of their first dose intake in the OLE Phase marks the end of their Core Phase treatment and study period.

OLE Phase
Treatment period: time from first study drug intake in the OLE Phase to 28 days after last dose of study drug intake in the OLE Phase.

Study period: time from first dose of study drug intake in the OLE Phase to the end of OLE Phase.

Combined Study Period
Treatment period: time from first dose of study drug intake (either HZN-825 or placebo) in the Core Phase to 28 days after the last dose in the OLE Phase.

Study period: time from first dose of study drug intake (either HZN-825 or placebo) in the Core Phase to the end of OLE Phase.

3.10.   Data Handling Conventions

Treatment of lab data transformations, handling of missing dates for AE and concomitant medication analysis, and other data handling conventions are described in the TLF shells document.

4.   SUBJECT DISPOSITION

4.1.   Subject Enrollment and Disposition

The number of subjects who are screened, randomized, and included in each analysis set will be presented. Patients who received study treatment, completed or discontinued from the study treatment will be presented based on the number of patients in each treatment group and overall for each study phase. Reasons for not completing the study or treatment will be summarized for each treatment group and for each study phase.

A summary of subject enrollment will be provided by treatment groups for individual investigators within each country, and overall based on the all subjects randomized set.

A similar enrollment table will be provided by randomization stratum based on the all subjects randomized set. The strata used for the randomization are as follows:

- Concomitant use of approved IPF therapy (yes vs no)
- FVC% predicted ($\geq$ 70 vs <70%)
- Prior use of approved IPF therapy (yes vs no)

The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects in applicable treatment group and overall. If there are discrepancies in the value used for stratification assignment between the Interactive Response Technology (IRT) and the clinical database, the value collected in IRT will be used in efficacy analysis. A listing of subjects with discrepancies in the value used for stratification assignment between the IRT and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the trial will be provided as an appendix to the CSR.

4.2.   Extent of Study Drug Exposure and Compliance

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol for each study phase and combined periods.

4.2.1.   Duration of Exposure to Study Drug

Total duration of exposure to study drug, defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, will be summarized by treatment groups using descriptive statistics. Handling of missing last study drug dosing date will be described in the TLF shells document.

4.2.2.   Compliance to Study Drug

The total number of doses administered will be summarized as continuous variables using descriptive statistics. Additionally, the total number of doses administered per subject will be summarized as a frequency distribution.

The presumed total number of doses administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

Total Number of Doses Administered =

$$\left(\sum \text{No. of Doses Dispensed} \right) - \left(\sum \text{No. of Doses Returned} \right)$$

4.2.2.1.   On-Treatment Adherence

The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}} \right) \times 100$$

Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories ($<80\%,\ 80-120\%,\ >120\%$) will be provided by treatment group.

No formal statistical testing is planned.

A by-subject listing of study drug administration (including both randomized and actual drug dispensed) and a separate drug accountability listing will be provided by subject ID number and visit. A listing of overall adherence will be provided as well, including any reasons for interruption of treatment.

4.3.   Protocol Deviations

Protocol deviations (PDs) occurring after subjects entered the trial are documented during routine monitoring. The number and percentage of subjects with major protocol deviations by deviation reason and subjects with protocol deviations related to COVID-19 will be summarized by treatment group for each study phase. A by-subject listing will be provided for eligibility criteria deviations and all other protocol deviations.

5.   BASELINE CHARACTERISTICS

Demographics, baseline characteristics and medical history will be summarized on the FAS and Safety analysis set for the Core Phase and OLE-SAF set for the OLE Phase.

5.1.   Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, sex, race, [age category <18, 18 - <65, 65 - ≤75, > 75], and ethnicity.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order by treatment group.

5.2.   Baseline Characteristics

Baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in kg/m^2), child-bearing potential (yes, no, not applicable), regions subjects were enrolled, and the stratification factors collected in the clinical database as well as in the IRT system will be summarized by treatment group. The stratification factors used for randomization are:

- The prior use of approved IPF therapy (i.e., nintedanib or pirfenidone, yes or no, stratification factor before Protocol Version 4.0)
- Concomitant use of approved IPF therapy (i.e., nintedanib or pirfenidone) (yes or no)
- FVC% predicted at Baseline ($\geq$ 70, <70)

Additional IPF history variables include: screening HRCT scan presence of: 10% - <50% parenchymal fibrosis (reticulation), < 25% honeycombing, or extent of fibrotic changes being greater than the extent of emphysema, baseline FVC % predicted categories (< 45%, 45% - 80%, > 80%), baseline forced expiratory volume in 1 second (FEV1)/FVC% predicted categories (< 0.7 and $\geq$ 0.7), and DLCO corrected for hemoglobin categories (< 25%, 25 – 90%, > 90%).

These baseline characteristics and IPF history variables will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables.

A by-subject listing of the above baseline characteristics will be provided by treatment group and subject ID number in ascending order.

A by subject listing of subjects' substance abuse data will be provided by subject ID and treatment group.

5.3.   Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

Medical history will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA), summarized and presented overall for the Safety Analysis Set by treatment group. Summaries will be presented alphabetically by system organ class (SOC) and, within a SOC, alphabetically by preferred term.

6. EFFICACY ANALYSES

6.1. Core Phase

6.1.1. Primary Efficacy Endpoint

6.1.1.1. Primary Analysis Method

The primary efficacy endpoint is the change from Baseline in FVC % predicted at Week 52. The FVC% predicted data are collected at Screening, Day 1, Week 4, Week 16, Week 28, Week 40, and Week 52.

The estimand for the primary efficacy analyses is constructed to compare the primary endpoint between each dose regimen of HZN-825 and placebo, using the treatment policy strategy approach to ICEs without data imputation in FAS subjects.

The primary analysis will be based on a mixed model for repeated measures (MMRM) analysis of covariance (ANCOVA) model using observed change in FVC % predicted values from all planned post-baseline assessments (Weeks 4, 16, 28, 40 and 52) with covariates of treatment group (300 mg HZN-825 QD, 300 mg HZN-825 BID, placebo), prior use of IPF therapy [yes or no], FVC% predicted at baseline [≥ 70, <70], visit week, and treatment by visit week interaction. An unstructured covariance matrix will be used as the primary analysis method; if the model does not converge, the following three variance-covariance matrices or by visit week will be attempted in order until one converges: heterogeneous Toeplitz (TOEPH), heterogeneous compound symmetry (CSH), and Toeplitz (TOEP).

Treatment group least squares means, associated standard error (SE) and their differences (each HZN-825 group minus placebo separately), SE of the difference, 90% CIs and p-values for each visit will be provided with Week 52 estimands being the primary efficacy endpoint result. A line plot of the LS mean value for FVC% predicted change from Baseline will be plotted by treatment group for each visit week over time, including the estimated 90% CI around each LS mean.

Change in FVC % predicted will also be summarized descriptively for observed cases at each visit.

6.1.1.2. Intercurrent Event Strategies

Potential intercurrent events (ICEs) such as early discontinuation from the treatment, rescue therapy uses during treatment, death, lung transplant, may occur during the trial.

Subjects who experience any of the ICEs including subjects with early discontinuations from treatment will be encouraged to stay in the trial after those ICEs occur, and data will be collected through planned study completion. In general, treatment policy strategy will be used to account for the ICEs for efficacy endpoints.

The estimand framework is summarized for the primary endpoint in Table 2.

Table 2. Estimand Framework for Primary Endpoint

Endpoint	Treatment	Population	Intercurrent Events (ICE) & ICE Strategy	Population-Level Summary
Change from Baseline in FVC % predicted at Week 52	HZN-825 300 mg BID, HZN-825 300 mg QD and Placebo	The Full Analysis Set	The intercurrent events which may impact analysis results include discontinuing from the treatment, initiating rescue therapy during treatment, death, lung transplant The treatment policy strategy will be used for aforementioned intercurrent events, which will closely reflect the real-world situation. All observed data will be used without missing data imputation. A mixed model for repeated measures (MMRM) will be fit to the data for the observed changes in FVC % predicted values from all planned post-baseline visits (Weeks 16, 28, 40 and 52). The least squares mean (LS mean) difference for the change from Baseline at Week 52 will be estimated from this model.	Point estimate (The least squares mean [LS mean] difference for the change from Baseline to Week 52 based on MMRM mixed model with its 90% confidence interval and P-value.

6.1.1.3.   Sensitivity Analyses

The following sensitivity analysis will be performed to assess the robustness of primary efficacy endpoint result.

Multiple Imputation

Multiple imputation will be carried out to impute the missing primary efficacy endpoint data based on two assumptions:

(1) Assuming treatment effect is preserved: imputation will be done under the assumption that missing data would be similar to subjects without missing data in the respective treatment group (HZN-825 300 mg QD, HZN-825 300 mg BID, placebo). Missing data due to subject death will be imputed using the worst outcome observed among all patients with available data.

(2) Assuming treatment effect is lost: imputation will be done under the assumption that missing data would be similar to subjects in the placebo group without missing data

Pattern mixture models (PMM) with the FCS imputation method will be used to impute missing primary efficacy endpoint in the above analyses. Missing data will be imputed based on Baseline FVC% predicted, treatment group and stratification factors used in randomization. One thousand imputed dataset will be created. For each imputed dataset, the

same model as defined for the primary analysis will be used. The results from each imputed dataset will be combined using Rubin's method.

Rank ANCOVA Analysis for Death

A rank ANCOVA analysis will be performed, assigning the worst rank to patients who died before week 52 visit. Missing data for reasons other than death will be imputed assuming treatment effect is preserved in respective treatment group. The covariates included in the analysis are treatment group, prior use of IPF therapy [yes or no], FVC% predicted at baseline [$\geq$ 70, <70].

6.1.1.4.   Supplementary Analyses

The effect of each dose regimen of HZN-825 will be compared to placebo using the following measurements and methods:

- Change in FVC (in mL) from Baseline to Week 52 using a similar MMRM analysis method as described in the primary analysis method.

- Cumulative response curve that displays a continuous view of the FVC% predicted change from baseline to Week 52 on the X-axis, with Y-axis displaying the proportion of subjects experiencing up to that level of change.

- While On-treatment Strategy for early treatment discontinuation: data collected after the treatment period (date of last dose + 28 days) will be excluded. The same model as for primary analysis will be used after excluding aforementioned data.

- Hypothetical strategy for lung transplant: the FVC% predicted to reflect the treatment effect is the value collected when lung transplant had not occurred. The same model as for the primary analysis will be used after excluding data collected after lung transplant. This analysis will be performed if we have more than three cases of lung transplant.

- Hypothetical strategy for rescue medication: the FVC% predicted to reflect the treatment effect is the value collected when rescue medication had not started. The same model as for the primary analysis will be used after excluding data collected after initiation of rescue medication.

6.1.2.   Secondary Efficacy Endpoints

6.1.2.1.   Key Secondary Endpoint: Proportion of Subjects with Decline in FVC% Predicted $\geq$10% from Baseline at Week 52

The proportion of subjects with a decrease in FVC% predicted $\geq$10% from baseline at Week 52 will be analyzed with observed data using a stratified logistic regression model. Baseline value and treatment will be considered as factors in the model and prior use of approved IPF therapy [yes or no], FVC% predicted at baseline [$\geq$ 70, <70] will be considered as stratification factors.

The odds ratio between each dose and placebo with its 90% confidence intervals and P-value will be presented. Subjects missing FVC% predicted values at Week 52 will be imputed as non-responders.

The proportion of subjects with a decrease in FVC% predicted ≥10% from baseline predicted will also be summarized descriptively for observed cases at each visit.

6.1.2.2.   Change From Baseline in the 6 Minute Walk Test (6MWT) Results to Week 52

The 6MWT measures the distance a subject can quickly walk on a flat, hard surface in 6 minutes (6-minute walk distance). This test evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units and muscle metabolism. The 6MWT will be performed according to American Thoracic Society (ATS) guidelines for the 6MWT (LH, 2018)

The distance walked by the 6MWT will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 6.1.1.1, but based only on observed data and including the covariate of oxygen flow rate in the model. For subjects who aren't on supplemental oxygen (SpO2) at the visit, 0 liters per minute will be imputed for their oxygen flow rate. Descriptive statistics for the observed results and change from Baseline in the absolute distance walked of the 6MWT will be summarized for each visit.

Values corresponding to the 6MWT including baseline (prior to test) dyspnea, baseline (prior to test) fatigue, baseline (prior to test) SpO2, baseline (prior to test) heart rate, end of test dyspnea, end of test fatigue, end of test heart rate, and end of test SpO2 will be summarized at each visit for the observed results and change from Baseline.

6.1.2.3.   Change from Baseline in King's Brief Interstitial Lung Disease (K-BILD) Questionnaire Total Score to Week 52

The K-BILD is a self-completed health status questionnaire comprising 15 items, each with a 7-point Likert response scale that was developed and validated specifically for patients with IPF (Patel AS, 2012). The response options vary, but in general 1 = worst disease impact and 7 = least disease impact. This questionnaire has 3 domains: psychological, breathlessness and activities and chest symptoms. The K-BILD domains and total score range from 0 to 100; 100 represents best health status.

The K-BILD scoring has recently changed with the introduction of a logit transformation step. The minimal clinically important difference for the K-BILD total score (logit version), as determined by both anchor and distribution-based methods, is a change of 5 units [Sinha et al., 2019].

The K-BILD total score will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 6.1.1.1, but based only on observed data.

Descriptive statistics for the observed results and change from Baseline in the K-BILD total score and each domain score will be summarized for each visit.

6.1.2.4. Change from Baseline in the Living with Pulmonary Fibrosis (L-IPF) Questionnaire Symptoms Total and Impacts Total Score to Week 52

The L-IPF is a validated questionnaire that assesses symptoms, disease impacts and health-related quality of life in subjects with IPF (Swigris JJ, 2020). This questionnaire was developed with input from the FDA and comprises 2 modules: a 15-item symptom module with 3 domains (dyspnea, cough and energy), all with a 24-hour recall, and a 20-item impacts module with 1-week recall. All items in both modules have response options in a 5-point (0-4) numerical rating scale format. The L-IPF yields five scales (symptoms total, dyspnea, cough, energy, and impacts total); raw scores for each are transformed to a model-based scale ranging from 0 to 100 with a mean of 50 and an SD of 10. For each scale, tables are used to convert raw scores, and higher scores indicate greater impairment.

The absolute change from Baseline in the L-IPF impacts total score, the L-IPF symptoms total score at week 52 will be computed and evaluated in the same manner as that described for the primary analysis of the primary endpoint in Section 6.1.1.1 but based only on observed data. Descriptive statistics for the observed results and change from baseline in the the L-IPF impact score, the L-IPF symptoms total score and the L-IPF symptoms domain scores will be summarized for each visit.

6.1.2.5. Change from Baseline in Leicester Cough Questionnaire (LCQ) Total Score to Week 52

The LCQ is a patient-reported questionnaire evaluating the impact of cough on quality of life. This questionnaire was originally developed for use in people with idiopathic chronic cough and has since been validated for use in people with bronchiectasis and chronic obstructive pulmonary disease (Birring SS, 2003).

The LCQ comprises 19 items and takes 5 to 10 minutes to complete. Each item assesses symptoms or the impact of symptoms over the last 2 weeks on a 7-point Likert scale. Scores in 3 domains (physical, psychological and social) are calculated as a mean for each domain (range: 1 to 7). A total score (range: 3 to 21) is also calculated by summing the domain scores. Higher scores indicate better quality of life.

The LCQ total score will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 6.1.1.1, but based only on observed data. Descriptive statistics for the observed results and change from Baseline in the LCQ total score and each domain score will be summarized for each visit.

6.1.2.6. Time to First Hospitalization Due to Respiratory Distress from Baseline up to Week 52

Hospitalization due to respiratory distress is defined as a non-elective hospitalization lasting more than 24 hours in a hospital, emergency room or observation unit, due to respiratory

causes that occur after randomization. Adverse events identified as leading to hospitalization due to respiratory distress will be adjudicated to confirm that the event and hospitalization meet the stated criteria.

A Cox proportional hazard model stratified by prior use of approved IPF therapy [yes or no] and FVC% predicted at baseline [≥ 70, <70] and treatment group as factors will provide the hazard ratio, its 90% CI and p-value to compare each HZN-825 group with the placebo group.

A subject will be considered as meeting the event criteria if the adjudication committee identifies any adverse event as leading to hospitalization due to respiratory distress. The start date of the hospitalization will be day of the event. In all other cases, the subject will be considered censored, and their last date of contact in the study (either date of safety follow-up if the subject doesn't enter the extension study or the Week 52 visit date for subjects that enter the extension) will be the date of censoring.

A corresponding Kaplan-Meier plot will be created to supplement the analysis, along with a summary of the quartiles of the Kaplan-Meier time to event estimate.

6.1.2.7. Composite Endpoint: Progression Free Survival (PFS) from Baseline up to Week 52, where Progression Includes Decline in FVC % Predicted ≥ 10% or Death

A Cox proportional hazard model stratified by concomitant use of approved IPF therapy [yes or no] and FVC% predicted at baseline [≥ 70, <70] and treatment group as factors will provide the hazard ratio, its 90% CI and p-value to compare each HZN-825 group with the placebo group.
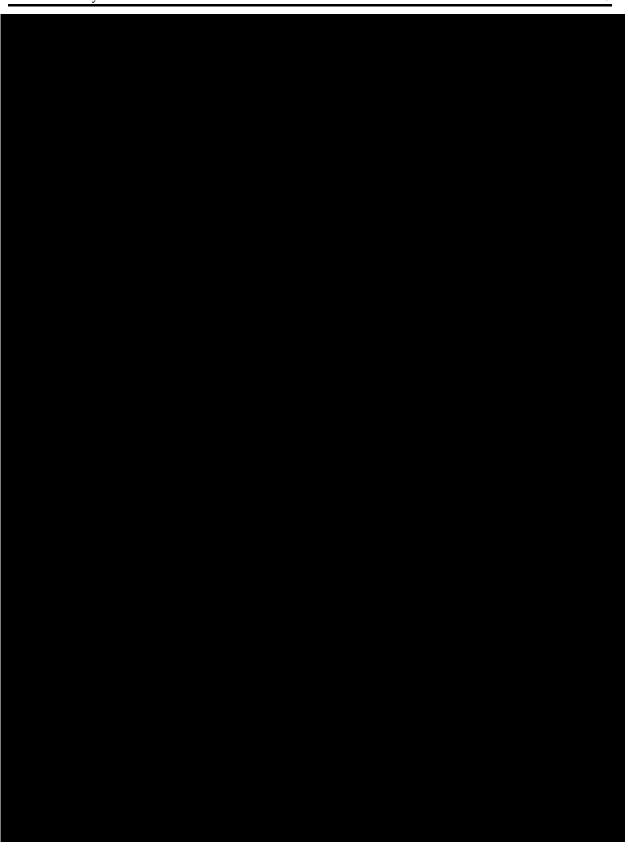
The time-to-progression will be defined as the duration from the date of first dose of study drug to either (a) the date of the visit where FVC % predicted declines ≥ 10% from Baseline or (b) the date of subject death, whichever occurs earlier. Subjects who do not experience either of these events will be considered censored at the time and their last date of contact in the study (either date of safety follow-up if the subject doesn't enter the extension study or the Week 52 visit date for subjects that enter the extension) will be the date of censoring.

A corresponding Kaplan Meier plot will be created to supplement the analysis.

6.1.3. Exploratory Endpoints

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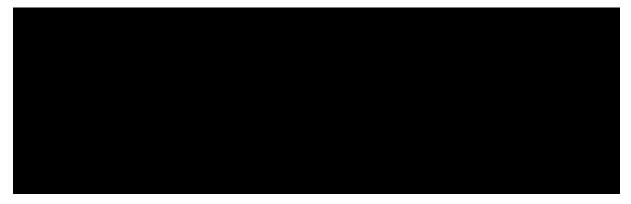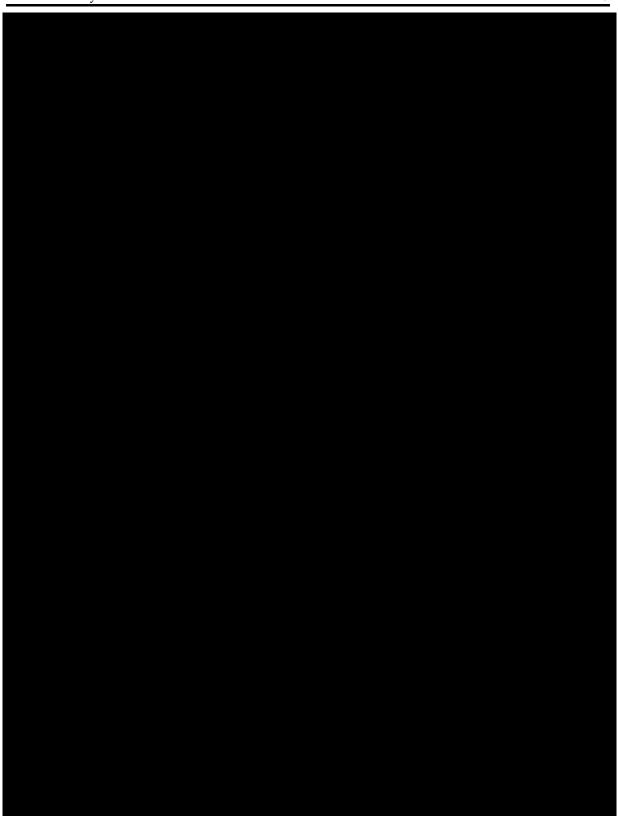
6.1.3.6.   Time to Death due to Respiratory Deterioration from Baseline up to Week 52

Events of death due to respiratory deterioration will be defined as adverse events with "Does this event represent a respiratory deterioration?" = "Yes" and with an outcome of "Fatal."

An analogous approach as described in Section 6.1.2.6 will be used to analyze this endpoint. If the number of event is rare at the end of the study, a listing will be provided instead of Kaplan Meier or Cox proportional hazard model.

6.2. Extension Phase

6.2.1. Primary Efficacy Endpoint

The primary endpoints for the OLE Phase are 1) the change from OLE Baseline to Week 104 FVC % predicted, 2) the change from HZN-825 Baseline to Week 104 FVC% predicted.

Primary efficacy endpoint will be summarized for each visit in the OLE-SAF analysis set using descriptive statistics, presented by the treatment group subjects were randomly assigned to in the Core Phase.

A mixed model for repeated measures (MMRM) will be fit to the data for descriptive purposes using observed change in FVC % predicted values from all planned post-trial OLE Baseline assessments (Weeks 68, 80, 92 and 104). A similar model that was used in the Core Phase will be used for the Extension Phase. An unstructured covariance matrix will be used for the primary analysis; if the model does not converge, other covariance matrices will be considered. The least squares mean (LS mean) difference in change from OLE Baseline to Week 104 from MMRM will be estimated from this model. For subjects with missing data at 1 or more time points, the available data will be included in the analysis.

6.2.2. Exploratory Endpoints

The following exploratory endpoints for the OLE Phase will be summarized using descriptive statistics by treatment group subjects were randomly assigned to in the Core Phase in OLE-SAF analysis set. Continuous variables will be summarized with mean, standard deviation, median, quartiles and range. Categorical variables will be summarized with subject counts and percentages. Time to event variables will be presented with Kaplan-Meier plots and estimates.

- Change from both OLE and HZN-825 Baselines in proportion of subjects with decline in FVC % predicted ≥10% at Week 104

- Change from both OLE and HZN-825 Baselines in the 6MWT results to Week 104

- Change from both OLE and HZN-825 Baselines in K-BILD scores to Week 104

- Change from both OLE and HZN-825 Baselines in L-IPF scores to Week 104

- Change from both OLE and HZN-825 Baselines in LCQ scores to Week 104

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- Time to first hospitalization due to respiratory distress from HZN-825 Baseline to Week 104

- Time to first onset of the composite endpoint of PFS from HZN-825 Baseline up to Week 104, where progression includes decline in FVC % predicted ≥10% from Baseline or death

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7.   SAFETY ANALYSES

Safety outcomes will be summarized descriptively for each study phase and combined periods. No inferential statistics are planned for safety outcomes. Safety analyses will be based on the Safety Analysis Set for the Core Phase, and OLE-SAF set for the OLE Phase and the combined periods.

7.1.   Adverse Events and Deaths

7.1.1.   Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2.   Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 according to the toxicity criteria specified in the protocol (Rheumatology Common Toxicity Criteria [RCTC] v2.0 (Woodworth T, 2007)). The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3.   Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Relationship to Study Treatment". Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4.   Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the trial protocol. SAEs captured and stored in the clinical database will be reconciled with the Horizon Global Safety database before data finalization.

7.1.5.   Summaries of Adverse Events and Deaths

Treatment emergent adverse events (TEAEs) are defined as adverse events occurring or worsening after the first dose of trial drug through 28 days after the last dose. For those patients who entered OLE Phase, date of their first dose in OLE Phase marks the end of reporting period for Core Phase.

Prior AEs are defined as any AE with a start date prior to the date of first dose of study treatment. Prior AEs will not be summarized, but will be included in listings.

7.1.5.1.   Summaries of AE Incidence

The incidence of following AEs will be summarized by SOC, PT, and treatment group for each study phase and the combined periods. Number and percentage of subjects who experienced events will be reported. AE summaries followed by an asterisk(*) will include the number of events and the corresponding exposure adjusted incidence rate:

1   TEAEs*

2   RCTC Grade 3 or higher TEAEs*

3   Serious TEAEs*

4   Treatment-related TEAEs*

5   TEAEs by maximum severity

6   Treatment-related TEAEs by maximum severity

7   Serious treatment-related TEAEs*

8   TEAEs assessed by the investigator as representing respiratory deterioration*

9   TEAEs assessed by the investigator as IPF-disease related*

10   TEAEs leading to permanent withdrawal of any trial drug*

11   TEAEs leading to death (ie, outcome of death)*

12   Subject incidence of AESIs: Orthostatic hypotension

Additionally, the frequency of TEAEs occurring in > 5% of subjects in any treatment group, serious TEAEs occurring in >3% of subjects in any treatment group, treatment-related serious TEAES occurring in >=2% of subjects in any treatment group, will be summarized by treatment group, primary SOC, and preferred term.

Multiple events will be counted only once per subject in each summary of subject counts. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending alphabetical order within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the trial.

In addition to the above summary tables, TEAEs and treatment-related TEAEs will be summarized by PT only in descending order of total frequency.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent

- SAEs

- Treatment-related serious TEAEs and non-serious TEAEs

- Deaths

- AEs leading to permanent withdrawal of trial drug

- Adjudicated AEs

- Adverse events of special interest: Orthostatic hypotension

7.1.6.   Adverse Events of Special Interest (AESI)

Orthostatic hypotension is the only AESI identified for this trial. Horizon will consider an event of orthostatic hypotension if the following definition is met: a reduction of systolic blood pressure by $\geq$20 mmHg or reduction of diastolic blood pressure by $\geq$10 mmHg at specific timepoints in the standing position and associated with symptoms such as lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, presyncope or syncope.

Any spontaneously reported signs or symptoms possibly associated with orthostatic hypotension will be captured as AEs. These will be identified based on the flag within the dataset and/or programmatically using the standard MedDRA query (SMQ) search criteria.

Results of the corresponding orthostatic hypotension assessment (when performed) will be listed.

7.2.   Laboratory Evaluations

Laboratory data collected during the trial will be analyzed and summarized using both quantitative and qualitative methods for each study phase and the combined periods. Laboratory results collected in conventional units will be converted to International System of Units (SI) for all summaries and listings. Laboratory parameters to be summarized are listed in Table 3.

Table 3. Lab Parameters

Chemistry	Hematology	Lipids and Coagulation	Urinalysis
Total protein, albumin, sodium, phosphate, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase, uric acid, glucose , lactate dehydrogenase; liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, total bile acid, total bilirubin, conjugated and unconjugated bilirubin, if applicable;	Hemoglobin, hematocrit, Red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, reticulocyte count White blood cells count and differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelets, and high sensitivity C-reactive Protein (hsCRP)	Lipids & Lipids (fasting): total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides Coagulation: prothrombin time, partial thromboplastin time, international normalized ratio and fibrinogen	Ketone, Specific Gravity, Urine Glucose, Urine Protein, Urobilinogen, blood, and pH

A listing of urine pregnancy test results will be produced.

A by-subject listing for laboratory test results will be provided by treatment, subject ID number, and time point in chronological order for hematology, serum chemistry, lipids and coagulation, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher based on the toxicity severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test specified in the trial protocol as follows:

1   Baseline values

2   Values at each postbaseline visit

3   Change from Baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from Baseline to a postbaseline visit will be defined as the visit value minus the baseline value.

7.2.2.   Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized by treatment group using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

1   Aspartate aminotransferase (AST): (a) > the upper limit of reference range (ULN); (b) > 3 x ULN; (c) > 5 x ULN; (d) > 8 x ULN; (e) >20 x ULN

2   Alanine aminotransferase (ALT): (a) > ULN; (b) > 3 x ULN; (c) > 5 x ULN; (d) > 8 x ULN; (e) >20 x ULN

3   Total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN; (c) > 3 x ULN

4   Alkaline phosphatase (ALP): (a) > 1.5 x ULN; (b) > 2.5 x ULN; (c) > 3 x ULN

5   Gamma Glutamyl Transferase (GGT): (a) > 2.5 x ULN; (b) > 5 x ULN; (c) > 20 x ULN

6   Potential Hy's Law: AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have non-missing postbaseline values of all relevant tests at the same postbaseline visit date.

A listing of subjects with elevated liver function test will be provided.

Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots will be produced.

7.2.3.   Shifts Relative to the Baseline Value

For hematology, chemistry, lipids and coagulation, results will be categorized as low, normal, or high based on their normal ranges. If toxicity grading is applicable to the laboratory result, toxicity grades will also be evaluated and assigned to the result. If available, shift tables using categories of toxicity grade comparing laboratory test results from Baseline to each visit will be presented with percentages based on subjects with a non-missing value at baseline and post-baseline visit. For toxicity grading where the grade can be assigned based on a low value and a high value, then both will be presented separately in the table summary.

If toxicity grade is not available, then categories of low, normal, and high will be used for the analogous presentation.

For urinalysis tests, results will be classified as normal or abnormal. Results out of range will be identified as such on subject listings. Shift tables for urinalysis results using categories of normal and abnormal, comparing laboratory test results from Baseline to each visit will be

presented with percentages based on subjects with a non-missing value at Baseline and post-baseline visit.

Shift plots may be produced for selected laboratory values.

7.3.   Body Weight, BMI and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, BMI and vital signs as follows:

1   Baseline value

2   Values at each postbaseline visit

3   Change from Baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from Baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection.

Descriptive summaries of observed and change from Baseline values will be presented for each vital sign parameter and weight by treatment group and visit for each study phase and combined periods. A shift table for vital signs by visit will be summarized.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. High or low values for vital signs will be flagged. Body weight, BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4.   Prior and Concomitant Medications

Medications collected at screening and during the trial will be coded using the current version of the World Health Organization (WHO) Drug dictionary for each study phase and combined periods.

7.4.1.   Prior Medications

Prior medications are defined as any medications taken with an end date prior to the date the subject took the first study drug.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 4 and preferred name using the number and percentage of subjects for each treatment group and overall for each study phase and combined periods. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered

alphabetically by ATC medical class and then alphabetically by preferred term within each ATC medical class.

7.4.2.   Concomitant Medications

Concomitant medications are defined as medications with a start date or stop date on or after the date of first study drug administration.

Use of concomitant medications and restricted medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 4 and preferred name using the number and percentage of subjects for each treatment group for each study phase and combined periods. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication.

All prior and concomitant medications (other than per-protocol study drugs) will also be provided in a by-subject listing.

7.5.   Electrocardiogram Results

ECG readings will be categorized into three categories by the investigators: normal, abnormal-not clinically significant and abnormal-clinically significant. Number and percentage of subjects in each categories will be reported by treatment group at each visit for each study phase and combined periods.

7.5.1.   Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results compared with baseline values will be presented by treatment group using the following categories: normal; abnormal-not clinically significant; abnormal-clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or post-baseline will not be included in the denominator for percentage calculation.

A by-subject listing for ECG assessment results will also be provided by subject ID and visit in chronological order.

7.5.2.   Corrected QT Intervals

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in msec; RR = 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds

The abnormal postdose QTcF interval values obtained during the trial will be summarized within the following categories:

- \> 450 msec

- \> 480 msec

- \> 500 msec

- QTcF increase from Baseline > 30 msec

- QTcF increase from Baseline > 60 msec

Percentages will be based on the number of subjects in the safety analysis set with at least one post-baseline value. Similar summaries will be provided by visit with the denominator based on the number of subjects with data at the given visit.

QTcF and uncorrected QT values at each visit and change from Baseline will be summarized for the Safety Analysis Set by treatment group using descriptive statistics.

7.5.3. Other ECG Values

HR, PR, QRS, and QT values at each visit and change from Baseline will be summarized by treatment group using descriptive statistics for each study phase and combined periods..

7.6. Other Safety Measures

An echocardiogram will be performed at Screening and at the Week 52 or the premature discontinuation visit. The results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated as CS or NCS by the investigator. Number and percentage of subjects in each category (Normal, Abnormal NCS, Abnormal CS) will be summarized by treatment group for each study phase and combined periods..

Percentages will be based on the number of subjects with an assessment completed. Echocardiogram results at screening and week 52 will also be provided in a listing.

8.   OTHER ANALYSES

There are no other analyses planned.

9.   PHARMACOKINETIC (PK) ANALYSES

During the Core Phase, blood samples will be collected from all subjects to evaluate the PK of HZN-825 and metabolite(s) at the following visits: Day 1 (at 2 to 4 hours after the first dose of trial drug), Week 4 (pre-dose), Week 10 (anytime during the visit), Weeks 16 and 28 (pre-dose and 2 to 4 hours post-dose) and Weeks 40 and 52 (pre-dose). For the Day 1, Week 16 and Week 28 Visits with post-dose PK samples, the morning dose regimen will be taken in the clinic. During the OLE Phase, blood samples will be collected at Week 52 (pre-dose), Week 56 (pre-dose and 2 to 4 hours post-dose) and Week 68, 80, 92 (pre-dose).

PK sample collection time and the most recent dosing time prior to PK sample collection will be recorded for all PK samples. The following presentations of subject plasma concentration data covered in this SAP will be provided for HZN-825 for the PK Analysis Set for Core Phase and OLE Phase:

- A listing including subject, visit, treatment and plasma concentrations.

- A table summary of plasma concentrations at each visit (number of samples observed, number of samples below limit of quantification, arithmetic mean, geometric mean, SD, coefficient of variation (CV)% calculated as 100% × SD/mean, minimum, 25th percentile, median, 75th percentile and maximum)

- Pre-dose PK samples will only be considered 'pre-dose' if they are collected within the 10-14 hours window post the most recent dose prior to the PK sample collection.

10.   REFERENCES

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11.   SOFTWARE

SAS® Software Version 9.4 or higher. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 8.5.1.0. Statistical Solutions, Cork, Ireland.

12. APPENDIX 1 SCHEDULE OF ASSESSMENTS

12.1. Schedule of Assessments During the Core Phase

Trial Visit	Screening[1]		Double-blind Treatment Period												Safety Follow-up Visit
Trial Visit	1	2		3	4	5	6	7	8	9	10	11	12	13	14 – 4 weeks after last dose of trial drug
Trial Week (W)	-56 days	-35 days	Day 1[2,3]	W2[4]	W4	W6[4]	W10	W16	W22[5]	W28[3]	W34[5]	W40	W46[5]	W52/PD[3,6]	W56
Visit Window (±days)				(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)
Informed consent[7]	X														
Lung HRCT (assessed by central review)[8]	X													X[9]	
Histopathology central review (assessed by central review, if available, but not required)[10]	X														
Review eligibility criteria		X	X												
Demographics		X													
Medical, IPF and substance abuse history		X	X												
Weight		X	X							X					
Height		X													
Randomization[11]			X												
Trial drug dispensing			X		X		X	X	X	X	X	X	X	X[12]	
Treatment compliance				X	X	X	X	X	X	X	X	X	X	X	
FVC % predicted/spirometry	X		X		X		X	X	X	X	X	X	X	X	
Titrated oxygen requirement			X					X		X		X		X	

	Screening[1]	Double-blind Treatment Period												Safety Follow-up Visit
Trial Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Trial Week (W)	−56 days to −35 days	Day 1[2,3]	W2[4]	W4	W6[4]	W10	W16	W22[5]	W28[3]	W34[5]	W40	W46[5]	W52/PD[3,6]	W56
Visit Window (±days)			(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)
6MWT		X					X		X		X		X	
DLCO[13]	X	X					X		X		X		X	
Patient-reported outcome assessments														
L-IPF, K-BILD, LCQ, SF-12		X					X		X		X		X	
Anchor questions														
FVC (last week)		X					X		X		X		X	
FVC (change since start of trial)									X				X	
Pregnancy test[14]	X	X		X		X			X	X	X		X	X
Physical examination[15]	X	X							X				X	
Vital signs, including pulse oximetry[16]	X	X		X		X	X	X	X	X	X	X	X	X
Orthostatic hypotension assessment		X		X					X				X	
12-lead electrocardiogram[17]	X	X					X		X				X	
Echocardiogram[17]	X												X	
Laboratory evaluations														
Chemistry and hematology[18, 19]	X	X				X	X	X	X	X	X	X	X	X
Fasting glucose and lipids[20]	X								X				X	
hsCRP		X							X				X	

Safety Follow-up Visit (Visit 14, W56): 4 weeks after last dose of trial drug

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Trial Visit	Screening[1]		Double-blind Treatment Period											Safety Follow-up Visit
Trial Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14
Trial Week (W) (±days)	-56 days	-35 days	Day 1 [2,3]	W2 [4]	W4	W6 [4]	W10	W16	W22 [5]	W28 [3]	W34 [5]	W40	W46 [5]	W52/PD [3,6]	W56
Visit Window (±days)				(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)
Urinalysis [18]	X		X		X		X	X	X	X	X	X	X	X	X
HBV and HCV serology	X														
HIV test [21]	X														
Adverse event assessment [22]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concom. medications [23]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
PK samples [24]			X		X		X	X	X	X		X		X	
Pharmacodynamic serum sample (collect pre-dose) [25]			X				X	X	X	X				X	
Pharmacogenetic sample (optional) [26]			X												
PBMC sample [27]			X							X				X	

6MWT=6-minute Walk Test; BID=twice daily; concom.=concomitant; CYP=cytochrome P450; DLCO=diffusing capacity of the lungs for carbon monoxide; FVC=forced vital capacity; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IPF=idiopathic pulmonary fibrosis; K-BILD= King's Brief Interstitial Lung Disease Questionnaire; L-IPF=Living with IPF; LCQ=Leicester Cough Questionnaire; LPAR1=lysophosphatidic acid receptor 1; PBMC=peripheral blood mononuclear cell; PD=premature discontinuation; PK=pharmacokinetic; QD=once daily; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SF-12=SF-12® Health Survey; SLCO=solute carrier organic anion transporter family member; W=Week; WOCBP=women of childbearing potential

1. Screening procedures can take place over more than 1 day/clinic visit provided consent is obtained first and all assessments are completed within the designated window. An abnormal test or assessment during Screening may be repeated once during the Screening Period.
2. On Day 1 (Baseline), subjects will be randomized and receive the first dose of trial drug in the clinic. All Day 1 assessments should be performed before the first dose of trial drug is administered in the clinic except for the PK sample collected 2–4 hours post dose.
3. Subjects should fast at least 8 hours prior to clinic visits on Day 1, Week 28 and Week 52 due to the need for fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides.
4. Remote (telephone) visit.
5. Visits may be conducted as home health visits, as available within local regions.

6. If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 52. If a subject prematurely discontinues trial drug and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 52 assessments. Subjects not entering the 52-week open-label Extension Phase will return to the clinic 4 weeks after the last dose of trial drug for a Safety Follow-up Visit.

7. Informed consent is required prior to performing any assessments, including submission of medical information for central review. Record date and time informed consent was given and who conducted the process on the appropriate source documentation and per required regulations.

8. Baseline lung HRCT will be performed only if no previous lung HRCT is available within the last 6 months prior to Screening date. This can be performed any time between the start of the initial 56 days of Screening and must be completed with results from central review vendor prior to Day 1. Confirm enough time for results to be made available from the central review vendor with turnaround time being up to 5 business days for results. Results are required from central review vendor.

9. The lung HRCT scan will be performed for all subjects within ±2 weeks of the Week 52/PD Visit. Central review will be performed.

10. Histopathology reports used towards IPF diagnosis (if available, but these are not required) will be submitted for central review.

11. Subjects will be randomized in a 1:1:1 ratio to receive HZN-825 300 mg QD, HZN-825 300 mg BID or placebo.

12. For subjects who are entering the open-label Extension Phase.

13. If SARS-CoV-2 exposure is of clinical concern for any subject, consider using a DLCO up to 6 months before the Screening Visit.

14. Perform for WOCBP. Serum pregnancy test at Screening and Week 52 (or as needed). Urine pregnancy tests should also be done every 4 weeks after randomization, which includes both in-clinic testing at scheduled visits prior to dosing (Weeks 1, 4, 16, 28 and 40) and at home (also a ±5-day window) by the subject and reported to the site (Weeks 8, 12, 20, 24, 32, 36, 44 and 48).

15. A complete physical examination will be performed, including, but not limited to, cardiac, pulmonary and neurologic assessments.

16. Vital signs (blood pressure, heart rate, respiratory rate, temperature, pulse oximetry) will be measured at each visit.

17. Additional electrocardiograms or echocardiograms will be conducted, if clinically indicated. An echocardiogram that has been performed within 3 months prior to Day 1 can serve as the Baseline echocardiogram if the subject has been clinically stable.

18. See Protocol Section 9.5.5.9 for details.

19. For subjects taking warfarin, physicians should monitor their international normalized ratio, as needed.

20. Includes fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides.

21. HIV testing is optional based on Investigator assessment, institutional practices or local guidelines to rule out suspected HIV or potential for a positive HIV result. Subject consent is required prior to HIV testing.

22. Adverse events that occur after signing the informed consent form and prior to dosing on Day 1 will be considered medical history. Adverse events occurring or worsening after the first dose of trial drug through the Safety Follow-up Visit will be considered treatment-emergent adverse events. All adverse events that occur from the signing of informed consent through the Safety Follow-up Visit will be recorded.

23. Includes recording of herb/supplement use. See Protocol Table 9.1 for restrictions regarding medications.

24. PK samples will be collected at each of the following visits: Day 1 (at 2 to 4 hours after the first dose of trial drug), Week 4 (pre-dose), Week 10 (anytime during the visit), Weeks 16 and 28 (pre-dose and 2 to 4 hours post-dose) and Weeks 40 and 52 (pre-dose for subjects entering the 52-week open-label Extension Phase). For the Day 1, Week 16 and Week 28 Visits with post-dose PK samples, the morning dose regimen will be taken in the clinic. Note: all pre-dose samples will be collected prior to any trial drug administration during the clinic visit; record date and time of last dose prior to visit. For subjects not entering the 52-week open-label Extension Phase, a sample will be collected anytime during the Week 52 Visit. Record date/time of all samples.

25. To be stored for future analysis. Use of stored serum sample for pharmacodynamic endpoints will be limited to understanding the trial drug as related to investigation of the LPAR₁ pathway or disease for the current trial.

26. This optional sample will be used to explore the impact of polymorphisms in genes encoding drug metabolizing enzymes and transporters (e.g., CYP2C9, CYP2D6, SLCO1B1 and SLCO1B3) on HZN-825 PK.

27. A blood sample for PBMCs will be collected on Day 1 (pre-dose), Week 28 (pre-dose) and Week 52 (pre-dose) for transcriptomic analysis.

12.2.   Schedule of Assessments During the Extension Phase

	Open-label Treatment Period										Safety Follow-up Visit
											4 weeks after last dose of HZN-825
Trial Visit	13	14	15	16	17	18	19	20	21	22	23
Trial Week (W)	W52[1]	W56	W62	W68	W74[2]	W80	W86[2]	W92	W98[2]	W104/PD[3]	
Visit Window (±days)	(±7)	(±5)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)
Informed consent[4]	X										
Review eligibility criteria	X										
Weight	X[5]					X				X	
HZN-825 dispensing	X	X	X	X		X		X			
Compliance	X	X	X	X	X	X	X	X	X	X	
Efficacy assessments											
FVC % predicted/ spirometry[6]	X[5]			X		X		X		X	
Titrated oxygen requirement	X[5]					X				X	
6MWT	X[5]					X				X	
Lung HRCT	X[5]									X[7]	
DLCO	X[5,8]					X[8]				X[8]	
Patient-reported outcome assessments											
L-IPF, K-BILD, LCQ, SF-12	X[5]					X				X	
Anchor questions											
FVC (last week)	X[5]					X				X	
FVC (change since start of trial)						X				X	
Clinical safety assessments											
Pregnancy test[9]	X[5]	X	X	X		X		X		X	X
Physical examination[10]	X[5]	X	X	X		X		X		X	X
Vital signs, including pulse oximetry[11]	X[5]	X	X	X		X		X		X	X
Orthostatic hypotension assessment	X[5]	X				X				X	
12-lead electrocardiogram[12]	X[5]	X				X				X	
Echocardiogram[12]	X[5]										
Clinical laboratory safety tests											
Chemistry and hematology[13, 14]	X[5]	X	X	X		X		X		X	X
Fasting glucose and lipids[15]	X[5]					X				X	
hsCRP	X[5]					X				X	
Urinalysis[16]	X[5]	X	X	X		X		X		X	X
PK samples[17]	X[5]	X		X		X		X			
Pharmacodynamic serum sample (collect pre-dose)[18]	X[5]					X				X	
PBMC samples (collect pre-dose)[19]	X[5]					X				X	

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	Open-label Treatment Period										Safety Follow-up Visit
											4 weeks after last dose of HZN-825
Trial Visit	13	14	15	16	17	18	19	20	21	22	23
Trial Week (W)	W52 [1]	W56	W62	W68	W74 [2]	W80	W86 [2]	W92	W98 [2]	W104/PD [3]	
Visit Window (±days)	(±7)	(±5)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications [20]	X [5]	X	X	X	X	X	X	X	X	X	X

6MWT=6-minute Walk Test; DLCO=diffusing capacity of the lungs for carbon monoxide; FVC=forced vital capacity; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IPF=idiopathic pulmonary fibrosis; K-BILD= King's Brief Interstitial Lung Disease Questionnaire; LCQ=Leicester Cough Questionnaire; L-IPF=Living with IPF; $LPAR_1$=lysophosphatidic acid receptor 1; PBMC=peripheral blood mononuclear cell; PD=premature discontinuation; PK=pharmacokinetic; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SF-12=SF-12® Health Survey; W=Week; WOCBP=women of childbearing potential

1. Subjects will receive the first dose of open-label HZN-825 in the Extension Phase in the clinic. Baseline assessments will be performed prior to dosing.
2. Remote (telephone) visit.
3. If a subject prematurely discontinues HZN-825, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 104. If a subject prematurely discontinues HZN-825 and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 104 assessments. Subjects will return to the clinic 4 weeks after the last dose of HZN-825 for a Safety Follow-up Visit.
4. Informed consent is required prior to performing any assessments in the Extension Phase. Record date and time informed consent was given and who conducted the process on the appropriate source documentation and per required regulations.
5. The result will be considered a Baseline value for this Extension Phase.
6. Except when strictly unavoidable, the same person should perform the assessment at each evaluation during the trial.
7. The HRCT scan should be performed within ±2 weeks of the Week 104/PD Visit.
8. The DLCO can be assessed within ±2-weeks of the Week 86 and Week 104/PD Visits.
9. Perform for WOCBP. Serum pregnancy test at Week 104 (or as needed). Urine pregnancy tests should also be done every 4 weeks after the Week 52 Visit, which includes both in-clinic testing at scheduled visits prior to dosing (Weeks 52, 56, 68, 80 and 92) and at home (also a ±7-day window) by the subject and reported to the site (Weeks 60, 64, 72, 76, 84, 88, 96 and 100).
10. A complete physical examination will be performed, including, but not limited to, cardiac, pulmonary and neurologic assessments.
11. Vital signs (blood pressure, heart rate, respiratory rate, temperature, pulse oximetry) will be measured at each clinic visit. The Week 52 vital sign assessment should be performed before the first dose of open-label HZN-825 is administered in the clinic.
12. Additional electrocardiograms or echocardiograms will be conducted, if clinically indicated. The Week 52 electrocardiogram should be performed before the first dose of open-label HZN-825 is administered in the clinic.
13. See Protocol Section 9.5.5.9 for details. Samples collected at the Week 52 Visit should be collected before the first dose of open-label HZN-825 is administered in the clinic.
14. For subjects taking warfarin, physicians should monitor their international normalized ratio, as needed.
15. Includes fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides.
16. See Protocol Section 9.5.5.9 for details.
17. PK samples will be collected at each of the following visits: Week 52 (pre-dose), Week 56 (pre-dose and 2 to 4 hours post-dose) and Week 68, 80, 92 (pre-dose). Note: all pre-dose samples will be collected prior to any HZN-825 administration for the day.
18. To be stored for future analysis. Use of stored serum sample for pharmacodynamic endpoints will be limited to understanding the trial drug as related to investigation of the $LPAR_1$ pathway or disease for the current trial.
19. A blood sample for PBMCs will be collected for transcriptomic analysis.
20. Includes recording of herb/supplement use. See Protocol Table 9.1 for restrictions regarding medications.

13.   APPENDIX 2 REVISION HISTORY AND APPROVALS

Effective Date	Version	Author	Description of Changes
26 Oct 2023	1.0	███████	Initial Version
16 Aug 2024	2.0	███████	Added additional analysis per FDA comments received on Jul 26, 2024: 1. Added a rank ANCOVA analysis for death as a sensitivity analysis 2. Added supplementary analysis for lung transplant 3. Added supplementary analysis for rescue medication 4. Moved "while on treatment strategy" from sensitivity analysis to supplementary analysis 5. Removed "early discontinuation from the trial", "adverse events leading to missing data", "Covid-19" from intercurrent events list

Confirmation by the study biostatistician (or designee), biostatistics management (or designee), and the study clinical colleague or therapeutic lead (or designee) that the review of this statistical analysis plan is complete, and there is agreement on the content.

Sr Manager, Biostatistics

Name,

Title

Signature/Date

Signed by:

Signer Name:
Signing Reason: I approve this document
Signing Time: 8/16/2024 | 2:47:37 PM GMT

Sr Director, Biostatistics

Signature/Date

Signed by:

Signer Name:
Signing Reason: I approve this document
Signing Time: 8/16/2024 | 2:59:13 PM GMT

Sr Medical Director, Clinical Development

Name,

Title

Signature/Date

Signed by:

Signer Name:
Signing Reason: I approve this document
Signing Time: 8/16/2024 | 2:56:14 PM GMT