CLINICAL TRIAL PROTOCOL FOR FIPAXALPARANT (HZN-825)

Protocol Number: HZNP-HZN-825-303
IND: 154671
EU CT Number: 2023-509784-24-00

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

Date: 07 October 2024

Version 5.0

Sponsor:
Horizon Therapeutics Ireland DAC (a wholly owned subsidiary of Amgen Inc.)
70 St. Stephen's Green
Dublin 2
D02 E2X4
Ireland

PROTOCOL

1 TITLE PAGE

Trial 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
Protocol Number:	HZNP-HZN-825-303
Version:	5.0
Investigational Product:	Fipaxalparant (HZN-825)
Indication:	Idiopathic pulmonary fibrosis
Sponsor:	Horizon Therapeutics Ireland DAC (a wholly owned subsidiary of Amgen Inc.) 70 St. Stephen's Green Dublin 2 D02 E2X4 Ireland
Development Phase:	2b
Sponsor's Responsible Medical Officer:	[redacted], MBBS, MD Senior Medical Director, Clinical Development (Rare Disease) Horizon Therapeutics USA., Inc. 1 Horizon Way Deerfield, IL 60015
Approval Date:	07 October 2024

CONTACT IN THE EVENT OF AN EMERGENCY

Any death, life-threatening event or other serious adverse event experienced by a subject during the course of the trial, whether or not judged drug-related, must be reported immediately and not later than 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF). If unable to access the eCRF, the event must be reported by submitting the completed Serious Adverse Event Form via email or fax to the contacts provided below.

US Fax:	1-888-814-8653 (toll free, within US)
Ex-US Fax:	+44 (0)207-136-1046
Email (worldwide):	svc-ags-in-us@amgen.com

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-HZN-825-303

Version: 5.0

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

Version Date: 07 October 2024

I agree to conduct the trial according to the protocol named above. I fully understand that any changes instituted by the Principal Investigator without previous discussion with the Sponsor constitute a violation of the protocol, unless necessary to eliminate an immediate hazard to the safety or well-being of a subject.

I acknowledge that I have read and understand the protocol named above and agree to carry out all of its terms in accordance with applicable regulations and laws.

I assure that the trial drug supplied by the Sponsor will be used only as described in the protocol named above.

Signature:

Name Trial Center Address City State Country	Date

SUMMARY OF CHANGES
Protocol HZNP-HZN-825-303
Protocol Version 4.0, Amendment 3 (01 December 2022) to Protocol Version 5.0, Amendment 4 (07 October 2024)

Key additions, revisions and clarifications to Version 5.0 of the protocol include:

- Updating to align with new company structure under new sponsor throughout.
- Updating numbers referring to safety and efficacy data to that from most recently completed studies.
- Adding the non-proprietary name (fipaxalparant) throughout the document.
- Align with European Union Clinical Trials (EU CT) submission requirements.
- Removing the sponsor signature page to align with new sponsor processes.
- Adding safety reporting language to align with new sponsor standard language.
- Updating Principal Investigator responsibilities to report serious breaches.
- Including definition of serious adverse events (SAEs), outcomes for reported adverse events (AEs)/SAEs/adverse events of special interest (AESIs) to align protocol information with revised Clinical SAE Report Form/electronic case report forms (eCRFs).
- Updated to Orthostatic Hypotension Assessment Manual v3.0 14 June 2023. The revisions in this manual from the prior version were previously communicated to all sites via memo on 12 June 2023.
- Added 17.10 Clinical SAE Report Form, 17.11 Clinical Trial Drug Exposure During Conception/Pregnancy Form, and 17.12 Lactation Notification Form to the appendix section.

Changes considered not key, minor wording changes, and correction of minor typographical errors are not detailed below.

SUMMARY TABLE OF CHANGES
Protocol Version 4.0, Amendment 3 (01 December 2022) to Protocol Version 5.0, Amendment 4 (07 October 2024)

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
Global HZN-825	**Global** fipaxalparant (HZN-825)	*To incorporate non-proprietary name throughout document*
Cover Page and Title Page Horizon Therapeutics Ireland DAC EudraCT Number: 2021-001253-32	**Cover Page and Title Page** Horizon Therapeutics Ireland DAC (a wholly owned subsidiary of Amgen Inc.) EU CT Number: 2023-509784-24-00	*To clarify new company structure*
Title Page Sponsor's Responsible Medical Officer and Signatory:	**Title Page** Sponsor's Responsible Medical Officer:	*To change the Sponsor's approver with shift to Amgen processes*
Title Page - Contact in the event of an emergency Any death, life-threatening event or other serious adverse event experienced by a subject during the course of the trial, whether or not judged drug-related, must be reported immediately, without undue delay, but not later than 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF).	**Title Page - Contact in the event of an emergency** Any death, life-threatening event or other serious adverse event experienced by a subject during the course of the trial, whether or not judged drug-related, must be reported immediately and not later than 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF).	*To align with new sponsor standard safety reporting language*
Title page US Fax: 800-860-7836 Ex-US Fax:+1-224-855-5055 Email:clinicalsafety@horizontherapeutics.com	**Title Page** US Fax: 1-888-814-8653 (toll free, within US) Ex-US Fax: +44 (0)207-136-1046 Email (worldwide):svc-ags-in-us@amgen.com	*To update with new company structure*
Sponsor Signature Page	Removed	*To change the Sponsor's approver with shift to Amgen processes*
2 Synopsis, Part 2 (Extension Phase), Safety Objective The safety objective is to examine the safety and tolerability of 52 weeks of open-label treatment with HZN-825 based on: •Treatment-emergent adverse event (TEAE) assessment •Concomitant medication use	**2 Synopsis, Part 2 (Extension Phase), Safety Objective** The safety objective is to examine the safety and tolerability of 52 weeks of open-label treatment with fipaxalparant (HZN 825) based on: •Treatment-emergent adverse event (TEAE) assessment •Concomitant medication use	*To remove repeated sentence*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
•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.	•Vital signs •12-lead electrocardiogram (ECG) •Clinical safety laboratory results	
2 Synopsis, Trial Design, Paragraph 5 An interim analysis with a futility analysis will be performed when [redacted] These unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC) and will be used to inform conduct of the Core Phase.	**2 Synopsis, Trial Design, Paragraph 5** An interim analysis with a futility analysis will be performed when [redacted] These unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC) and will be used to inform conduct of the current trial.	*To update the current trial.*
2 Synopsis, Exclusion Criteria, Item 5 5.Use of any of the following therapies within 4 weeks prior to Screening, during the Screening Period or planned during the trial: prednisone at steady dose >10 mg/day or equivalent or cyclosporine. Prednisone ≤10 mg/day (or equivalent dosing of glucocorticoids) is allowed.	**2 Synopsis, Exclusion Criteria, Item 5** 5.Use of any of the following therapies within 4 weeks prior to Screening, during the Screening Period or planned during the trial: prednisone at steady dose >10 mg/day or equivalent or cyclosporine.	*To remove the allowance of prednisone ≤10 mg/day (or equivalent dosing of glucocorticoids) in the study.*
2.2 Schedule of Assessments During the Extension Phase, Footnote 8 The DLCO can be assessed within ±2-weeks of the Week 86 and Week 104/PD Visits.	**2.2 Schedule of Assessments During the Extension Phase, Footnote** 8 The DLCO is required for Week 80 and Week 104/PD Visits.	*To update the appropriate week and requirement diffusing capacity of the lungs for carbon monoxide (DLCO)*
7.1.3.4 Clinical Experience, Paragraphs 1 and 4 HZN-825 has been administered to 102 healthy subjects in 6 completed Phase 1 clinical trials and 31 subjects with diffuse cutaneous SSc in a Phase 2a clinical trial. In clinical trials completed as of 28 February 2022, HZN-825 was well-tolerated and showed similar safety and PK profiles across healthy subjects (including elderly healthy subjects) and subjects with diffuse cutaneous SSc.	**7.1.3.4 Clinical Experience, Paragraphs 1 and 4** Fipaxalparant (HZN-825) has been administered to 244 healthy subjects in nine Phase 1 completed clinical trials and 31 subjects with diffuse cutaneous SSc in a Phase 2a clinical trial. In clinical trials completed, as provided in the current version of the Investigator's Brochure, fipaxalparant (HZN-825) was well-tolerated and showed similar safety and pharmacokinetic profiles across healthy subjects (including	*To update numbers based on most recently completed studies.* *To update information about elevated transaminases being observed in clinical studies with Investigational Product.*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
Based on safety results to date, orthostatic hypotension is identified as a potential risk of HZN825 therapy that will continue to be monitored as an AE of special interest (AESI) (Section 9.5.5.1.1.4).	elderly healthy subjects) and subjects with diffuse cutaneous SSc. Based on safety results to date, orthostatic hypotension is identified as a potential risk of fipaxalparant (HZN-825) therapy that will continue to be monitored as an AE of special interest (AESI) (Section 9.5.5.1.1.4). Additionally, increases in hepatic transaminases have been seen in blinded clinical studies with fipaxalparant (HZN-825). These events are mostly non-serious and reversible. Liver enzyme elevation will be monitored per FDA guidelines (Section 9.3.3.1)	
7.1.3.5 Benefit/Risk Assessment, Paragraph 2 Based on the cumulative safety data available to date on HZN-825 orthostatic hypotension, drug-drug interactions, embryo-fetal toxicity and liver toxicity are considered as important potential risks.	**7.1.3.5 Benefit/Risk Assessment, Paragraph 2** Based on the cumulative safety data available to date on fipaxalparant (HZN-825), transaminase increase has been evaluated as an important identified risk and orthostatic hypotension, drug-drug interactions, and embryo-fetal toxicity are considered as important potential risks.	*To update the risk of elevated transaminases and removal of liver toxicity.*
7.3 Rationale for Dose Selection, Paragraph 1 The dose regimens to be evaluated in this trial are 300 mg QD and 300 mg BID with a meal using HZN-825 tablets manufactured by [redacted].	**7.3 Rationale for Dose Selection, Paragraph 1** The dose regimens to be evaluated in this trial are 300 mg QD and 300 mg BID with a meal using fipaxalparant (HZN-825) tablets manufactured by [redacted]	*To add a new manufacturer of the HZN-825 investigational product that may be used during the conduct of the trial.*
9.3.3.1.1 Removal of Subjects from Trial Drug, Bullet 2 Subjects who have ALT or AST levels >3 × ULN confirmed in a repeat test need to undergo close observation as prescribed by the FDA guidance on drug-induced liver injury. Close observation includes repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic. At the discretion of the Investigator the trial drug can be continued during this close observation.	**9.3.3.1.1 Removal of Subjects from Trial Drug, Bullet 2** Subjects who have ALT or AST levels >3 × ULN confirmed in a repeat test need to undergo close observation as prescribed by the FDA guidance on drug-induced liver injury. Close observation includes repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic. The decision to rechallenge the subject is to be discussed and agreed upon by the investigator, and Amgen Medical Monitor.	*To update the decision to rechallenge a subject.*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
9.4.6.1.2 Drug-induced Liver Injury Refer to Section 9.3.3.1 for criteria regarding trial drug discontinuation due to drug-induced liver injury.	**9.4.6.1.2 Drug-induced Liver Injury** Elevated hepatic transaminases have been evaluated to be an important identified risk with fipaxalparant (HZN-825). The events are mostly non-serious and transient. Refer to Section 9.3.3.1 for criteria regarding trial drug discontinuation due to drug-induced liver injury.	*To update the information about elevated transaminases.*
9.5.1.6.5 Exit Interviews To understand what subjects perceive as meaningful in terms of change in some of the patient-reported outcome measures during the Core Phase of the trial, semi-structured qualitative interviews will be conducted by telephone after the Week 52 Visit (trial exit) at 4 to 5 sites (approximately 20 subjects) across the US. Subjects in the exit interviews will be selected in order to approximate representativeness of the clinical trial population of patients with IPF, with diversity in terms of age, gender, ethnicity, urban/rural practice and geographic area of residence, where possible. The one-on-one, semi structured, qualitative interviews will provide a greater understanding of the subjects' treatment experience and meaningful change in select patient-reported endpoints. These interviews are covered and conducted under a separate protocol, and are not part of the schedule of assessments for HZNP-HZN-825-303.	**9.5.1.6.5 Exit Interviews** Section deleted.	*Section deleted*
9.5.5.1.1.4 Adverse Events of Special Interest, Paragraph s 2, 3 and 5 The following AESI is identified for this trial: •Orthostatic hypotension. The Sponsor will consider an event of orthostatic hypotension if the following definition is met: a reduction of systolic blood pressure by ≥20 mmHg or reduction of diastolic blood pressure by ≥10 mmHg and associated with symptoms such as lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea,	**9.5.5.1.1.4 Adverse Events of Special Interest, Paragraphs 2, 3 and 5** The following AESI is identified for this trial: •Orthostatic hypotension. The Sponsor will consider an event of orthostatic hypotension if the following definition is met: a reduction of systolic blood pressure by ≥20 mmHg or reduction of diastolic blood pressure by ≥10 mmHg **and** associated with symptoms such as lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea,	*To update the eligibility of Adverse Events (AE) while subject is going through Orthostatic hypotension assessment.*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
palpitations, tremulousness, headache, presyncope or syncope. Orthostatic hypotension assessment procedure will be performed during the Core Phase (as outlined in Section 2.1 on Day 1 and at Weeks 4, 28 and 52/premature discontinuation) and the Extension Phase (as outlined in Section 2.2 on Day 1 [Week 52 of Core Phase] and at Weeks 56, 80 and 104/premature discontinuation), as is detailed in the Orthostatic Hypotension Assessment Manual in Section 17.9. ~~If any symptoms occur during the assessment in combination with the blood pressure reductions noted above, they are considered as part of the orthostatic hypotension event and will not be recorded separately as individual AEs.~~ If symptoms are reported by the subject throughout the assessment, without the blood pressure reductions noted above, then the symptoms will be recorded separately as AEs and orthostatic hypotension will not be recorded.	palpitations, tremulousness, headache, presyncope or syncope. The symptoms i.e., lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, presyncope or syncope are reported by the patient throughout the orthostatic hypotension assessment, without the BP reductions (reduction of systolic BP ≥ 20 mmHg or diastolic BP ≥10 mmHg), then these symptoms will be recorded as AE. Please note that the above-mentioned reported symptoms during orthostatic hypotension assessment should only be reported as adverse events separately if they meet any of the below criteria: • The symptoms are severe and/or require medical interventions • The symptoms triggered by the orthostatic hypotension assessment maneuver and persisted for a significantly longer duration beyond the orthostatic hypotension assessment period • The symptoms are assessed not due to the maneuver of orthostatic hypotension assessment If these symptoms are reported in combination with the BP reductions, i.e., reduction of systolic BP ≥20 mmHg or diastolic BP ≥10 mmHg, these symptoms will be considered part of the orthostatic hypotension event and will not be reported separately. Orthostatic hypotension assessment procedure will be performed during the Core Phase (as outlined in Section 2.1 on Day 1 and at Weeks 4, 28, and 52/premature discontinuation) and the Extension Phase (as outlined in Section 2.2 on Day 1 [Week 52 of Core Phase] and at Weeks 56, 80, and 104/premature discontinuation), as is	

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
	detailed in the Orthostatic Hypotension Assessment Manual in Section 17.9. If symptoms are reported by the subject throughout the assessment, without the BP reductions noted above, then the symptoms will be recorded separately as AEs and orthostatic hypotension will not be recorded.	
9.5.5.1.2 Documentation of Adverse Events If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by trial drug, the Investigator will report this SAE using the procedures described in Section 9.5.5.1.5. Detailed information regarding all SAEs must also be recorded on the Serious Adverse Event Reporting Form. Whenever clinically appropriate, the Investigator should group together into a single term the signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis. and sneezing might be grouped together as "upper respiratory infection" if the Investigator is confident of the diagnosis.	**9.5.5.1.2 Documentation of Adverse Events** If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by trial drug, the Investigator will report this SAE using the procedures described in Section 9.5.5.1.5. The Investigator is responsible for collecting and documenting the outcome of AEs/SAEs. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, except for the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.	*To align with expected reporting and subject confidentiality*
9.5.5.1.4 Relationship or Causality to Trial Drug The relationship of the trial drug to each AE will be determined by the Investigator and the Sponsor based on the following definitions: •Not related: There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event. •Related: There is evidence in favor of a causal relationship (i.e., there is a plausible time course) and at least one of the following criteria apply: ▪ There is a reasonable pharmacological relationship (or known class effect). ▪ There is no other more plausible explanation. ▪ There is a positive de-challenge (without active treatment of the event).	**9.5.5.1.4 Relationship or Causality to Trial Drug** The investigator is obligated to assess the relationship between investigational product(s) and each occurrence of each AE and SAE. Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in their assessment.	*To align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
▪ There is a positive re-challenge. ▪ There is a distinguishable dose effect.	For each AE/SAE, the investigator must document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which a SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data. The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The relationship of the trial drug to each AE will be determined by the Investigator and the Sponsor based on the following definitions: •Not related: There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event. •Related: There is evidence in favor of a causal relationship (i.e., there is a plausible time course) and at least one of the following criteria apply: ▪ There is a reasonable pharmacological relationship (or known class effect). ▪ There is no other more plausible explanation. ▪ There is a positive de-challenge (without active treatment of the event). ▪ There is a positive re-challenge. ▪ There is a distinguishable dose effect.	
9.5.5.1.5 Reporting and Documenting Serious Adverse Events All SAEs beginning with the time of signing of the ICF and continuing through 4 weeks after the last dose of trial drug must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to trial drug: 1. Report the SAE to the Sponsor by entering the information into the eCRF **immediately, without undue**	**9.5.5.1.5 Reporting and Documenting Serious Adverse Events** All SAEs beginning with the time of signing of the ICF and continuing through 4 weeks after the last dose of trial drug must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to trial drug:	*To align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
delay but not later than 24 hours after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form **immediately, without undue delay but not later than 24 hours** after becoming aware that a subject has experienced an SAE (see Section 17.1 for contact information). 2. Perform appropriate diagnostic tests and therapeutic measures and submit all follow up substantiating data, such as diagnostic test reports, hospital discharge summaries and autopsy report to the Sponsor's representative. 3. Conduct appropriate consultation and follow-up evaluation until the SAE outcome is known or the SAE is resolved. 4. Review each SAE report and evaluate the relationship of the SAE to trial treatment.	1. Report the SAE to the Sponsor by entering the information into the eCRF **immediately and not later than 24 hours** after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE Reporting form **immediately and not later than 24 hours** after becoming aware that a subject has experienced an SAE (see Section 17.1 for contact information). After the study is completed at a given site, the electronic data capture (EDC) system will be taken off-line to prevent the entry of new data or changes to existing data. If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the EDC system has been taken off-line, then the site can report this information on the paper-based SAE Form. 2. Perform appropriate diagnostic tests and therapeutic measures and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries and autopsy report to the Sponsor's representative. 3. Conduct appropriate consultation and follow-up evaluation until the SAE outcome is known or the SAE is resolved. Outcomes for reported AEs/SAEs/AESIs are to be defined as follows: •Recovering/Resolving •Recovered/Resolved •Not Recovered/Not Resolved •Recovered/Resolved with sequelae •Fatal •Unknown	

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
	4. All new information for previously reported SAEs must be sent to the Sponsor **immediately and no later than 24 hours** after investigator's awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the SAE must be consistent with that recorded on the Adverse Events eCRF. There is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of SAEs suspected to be related to investigational product, then these SAEs will be reported to the Sponsor **immediately and no later than 24 hours** after the investigator's awareness of the event. Serious adverse events reported after the end of the study will be captured within the safety database as clinical study cases and handled accordingly based on relationship to investigational product. If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study. Review each SAE report and evaluate the relationship of the SAE to trial treatment.	
9.5.5.1.6 Follow-up of Adverse Events The Investigator is obligated to follow up any reported AE, SAE or AESI until all relevant clinical data are known to allow for an outcome or the event is resolved, in addition to confirming the causality assessment. Any ongoing trial drug-related AE present at the time of trial termination, including a clinically significant laboratory test abnormality,	**9.5.5.1.6 Follow-up of Adverse Events** The Investigator is obligated to follow-up any reported AE, SAE or AESI until all relevant clinical data are known to allow for an outcome or the event is resolved, in addition to confirming the causality assessment. Any ongoing trial drug-related AE present at the time of trial termination, including a clinically significant laboratory test abnormality,	*To align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
will be followed until the event is resolved or until the outcome is known.	will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained. The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. If a subject is permanently withdrawn from investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a SAE, this information must be submitted to Sponsor. The investigator will submit any updated SAE data to Sponsor **immediately and no later than 24 hours** of receipt of the information.	

9.5.5.1.10 Development Safety Update Reports The Sponsor will prepare and submit annual safety reports to the US FDA. Drug safety update reports will also be submitted to countries and territories as required.	**9.5.5.1.10 Development Safety Update Reports** The Sponsor will prepare and submit annual safety reports to the FDA. Drug safety update reports will also be submitted to countries and territories as required. The Sponsor will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report in the European Union) for the Sponsor Investigational Product. To ensure that consolidated safety information for the study is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical study, if applicable. **9.5.5.1.11 Regulatory Reporting Requirements for Safety Information** If subject is permanently withdrawn from investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a SAE, this information must be submitted to the Sponsor. Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the external review body and investigators. Individual safety reports for suspected unexpected serious adverse reactions will be reported by the Sponsor according to local regulatory requirements (e.g., electronic submission to the Eudravigilance database in the EU as per EU Clinical Trial Regulation 536/2014) as well as Sponsor policy and forwarded to investigators as necessary.	*To add the development safety update report to align with recommendations from regulatory agencies and additional sections to align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
	An investigator who receives an individual safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the external review body, if appropriate according to local requirements. For studies in which the treatment assignment is blinded, to comply with worldwide reporting regulations for SAEs, the treatment assignment of subjects who develop serious, unexpected, and related AEs may be unblinded by the Sponsor before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related SAEs reports sent to regulatory authorities in accordance with local requirements. **9.5.5.1.12 Safety Monitoring Plan** Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.	
9.5.5.2 Pregnancy Reporting The Investigator should report pregnancies to the Sponsor within 24 hours by submitting the completed pregnancy report form by email to clinicalsafety@horizontherapeutics.com, fax or telephone within 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see Section 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy. If pregnancy continues and the subject signs the pregnancy consent form, monitoring should also continue to the conclusion of the pregnancy and the outcome of the pregnancy should be reported to the Sponsor.	**9.5.5.2 Pregnancy and Lactation Reporting** Details of all pregnancies and/or lactation in female subjects and pregnancies in female partners of male subjects will be collected after the start of study treatment and until 4 weeks after last dose of trial drug. If a pregnancy is reported, the investigator is to inform the Sponsor **immediately and no later than 24 hours** of learning of the pregnancy and/or lactation. The Investigator should report pregnancies to the Sponsor by submitting the completed PRF **immediately and not later than 24 hours** after becoming aware that the subject/subject's female partner has become pregnant (see Appendix 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy.	*To align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
	If pregnancy continues and the subject signs the pregnancy consent form, monitoring should also continue to the conclusion of the pregnancy and the outcome of the pregnancy should be reported to the Sponsor. Lactation information will be recorded on the Lactation Notification Form and submitted to Sponsor Global Patient Safety **immediately and no later than 24 hours** of the investigator's awareness of the event.	
12 Trial Monitoring Every effort will be made to maintain the anonymity and confidentiality of subjects participating in this clinical trial. However, because of the investigational nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, its designated agents and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this trial and to have direct access to inspect, for purposes of verification, the hospital or clinical records of all subjects enrolled in this trial. A statement to this effect should be included in the ICF.	**12 Trial Monitoring** Every effort will be made to maintain the anonymity and confidentiality of subjects participating in this clinical trial. However, because of the investigational nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, its designated agents and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this trial and to have direct access to inspect, for purposes of verification, the hospital or clinical records of all subjects enrolled in this trial. A statement to this effect should be included in the ICF. Serious Breach Suspected Serious Breaches must be reported to the study team (e.g., Clinical Monitor) or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness. A Serious Breach is a breach of any of the following: • GCP • the clinical trial protocol • an applicable regulation That is likely to impact to a significant degree either of the following:	*To update requirements for Principal Investigator's (PI) responsibilities to report serious breaches per regulatory recommendations*

Text Version 4.0, Amendment 3 01 December 2022	Amended Text Version 5.0, Amendment 4 07 October 2024	Reason for Change
	• the safety, physical, or mental integrity and the rights of the participant • the reliability and robustness of the data and the scientific value of the trial	
17.9 Orthostatic Hypotension Assessment Manual Version 2.0	**17.9 Orthostatic Hypotension Assessment Manual** Version 3.0	*To update the symptoms reported during the orthostatic hypotension assessment will only be recorded as adverse events if they are severe, persist beyond the assessment, or are unrelated to the assessment maneuver, unless accompanied by significant blood pressure reductions.*

2 SYNOPSIS

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	
Protocol Number: HZNP-HZN-825-303	**Phase:** 2b
Protocol Version: 5.0	
Test Drug: Fipaxalparant **(**HZN-825)	**Indication**: Idiopathic pulmonary fibrosis
Number and Geographical Regions of Trial Sites: Approximately 85 trial sites in North America, Europe, South America, Africa, Asia (including Japan), and Australia	

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).

Part 1 (Core Phase)

The overall objective of the Core Phase is to investigate the efficacy, safety, and tolerability of 2 dose regimens of fipaxalparant (HZN-825), a selective antagonist of lysophosphatidic acid receptor 1 ($LPAR_1$), administered once daily (QD) or twice daily (BID) for 52 weeks in the treatment of subjects with idiopathic pulmonary fibrosis (IPF).

Primary Objective

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

Secondary Objectives

1. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the proportion of subjects with decline in FVC % predicted ≥10% from Baseline after 52 weeks of treatment.
2. Evaluate the effect of 2 dose regimens of fipaxalparant (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 fipaxalparant (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 fipaxalparant (HZN-825) versus placebo on the Living with IPF (L-IPF) after 52 weeks of treatment.
5. Evaluate the effect of 2 dose regimens fipaxalparant (HZN-825) versus placebo on the Leicester Cough Questionnaire (LCQ) after 52 weeks of treatment.
6. Evaluate the effect of 2 dose regimens of fipaxalparant (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 fipaxalparant (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 fipaxalparant (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 fipaxalparant (HZN-825).

Exploratory Objectives

1. [redacted]
2.
3.

4. [redacted]
5. [redacted]
6. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on mortality due to respiratory deterioration up to 52 weeks of treatment.
7. [redacted]
8. [redacted]

Part 2 (Extension Phase)

The overall objective of the Extension Phase is to investigate the long-term efficacy, safety, and tolerability of fipaxalparant (HZN-825), a selective antagonist of $LPAR_1$, 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 fipaxalparant (HZN-825) in the Extension Phase
- Fipaxalparant (HZN-825) Baseline, defined as the latest measurement prior to the first dose of fipaxalparant (HZN-825) in either the Core Phase or the Extension Phase. For subjects who received placebo in the Core Phase, OLE Baseline will be the same as fipaxalparant (HZN-825) Baseline.

Primary Objective

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

Safety Objective

The safety objective is to examine the safety and tolerability of 52 weeks of open-label treatment with fipaxalparant (HZN-825) based on:

- Treatment-emergent adverse event (TEAE) assessment
- Concomitant medication use
- Vital signs
- 12-lead electrocardiogram (ECG)
- Clinical safety laboratory results

Exploratory Objectives

The exploratory efficacy objective is to evaluate the efficacy of 52 weeks of open-label treatment with fipaxalparant (HZN-825) via additional efficacy measurements:

- Proportion of subjects with decline in FVC % predicted ≥10%
- 6MWT
- K-BILD
- L-IPF
- LCQ

- [redacted]

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

Trial Design:

HZNP-HZN-825-303 (HARBOR) 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 fipaxalparant (HZN-825) in subjects with IPF. Part 2 (Extension Phase) is an optional, open-label, repeat-dose, multicenter extension of the Core Phase. The trial will include up to an 8-week Screening Period and a 52-week Double-blind Treatment Period in the Core Phase and 52 weeks of open-label fipaxalparant (HZN-825) treatment in the Extension Phase.

During the Core Phase, subjects will be screened within 8 weeks prior to the Baseline (Day 1) Visit. Approximately 135 subjects who meet the trial eligibility criteria will be randomly assigned in a 1:1:1 ratio on Day 1 to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (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%

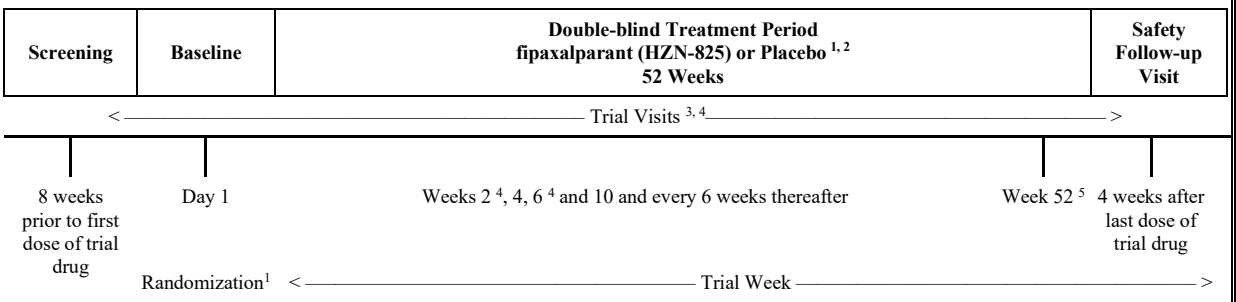
During the Core Phase, subjects will take their first dose of trial drug at the clinic on Day 1 (Week 0) and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating 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 [redacted] These unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC) and will be used to inform 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. A Horizon unblinded team may also aid in dose selection and future trial design.

Subjects who complete the 52-week Double blind Treatment Period of the Core Phase of the trial will be invited to extend their participation in the 52-week Extension Phase of the trial, for a total exposure to trial drug of 104 weeks. 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.

An overview of the trial design is presented below.

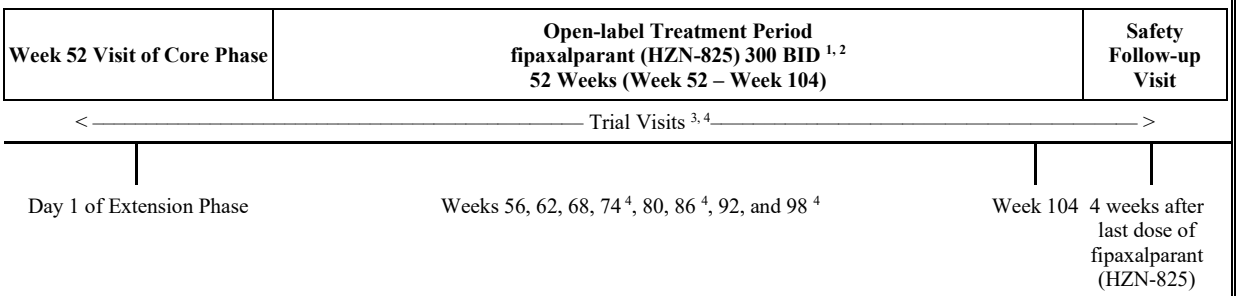
Core Phase



BID=twice daily; QD=once daily

1. Subjects will be randomized in a 1:1:1 ratio to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (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 the 52-week Extension Phase of the trial.

Extension Phase



BID=twice daily

1. The fipaxalparant (HZN-825) dose may be modified based on the results of the Core Phase.
2. If a subject prematurely discontinues open-label fipaxalparant (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 fipaxalparant (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.

Subject Population:
Approximately 135 subjects ≥18 years of age with IPF will be enrolled.

Eligibility Criteria for the Core Phase:

Inclusion Criteria:
Eligible subjects must meet/provide **all** of the following criteria:

1. Written informed consent.
2. Male or female ≥18 years of age at Screening.
3. Current diagnosis of IPF, as defined by American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) guidelines [Raghu et al., 2022] and determined by central review; the date of initial diagnosis of IPF should be ≤7 years prior to Screening.

4. No recent changes or planned changes to the dose or regimen for IPF therapy, defined as:
   - Receiving a stable dose of IPF-approved therapy (i.e., nintedanib or pirfenidone) for a minimum of 3 months prior to Day 1 with no plans to change the background regimen during trial participation, or
   - Not currently receiving background IPF-approved therapy at Screening (either naïve to IPF-approved therapy or previously discontinued any IPF-approved therapy at least 4 weeks prior to Day 1 or drug-specific, 5 half-lives elimination period if longer than 4 weeks), and with no current plans to restart treatment during trial participation
   - Subjects receiving any additional agent for IPF therapy must be on a stable regimen for at least 3 months prior to Day 1 with no current plans to change the treatment regimen during trial participation. Any previously discontinued therapy used to treat IPF must have been discontinued at least 4 weeks prior to Day 1 or 5 half-lives for that specific therapy must have elapsed, whichever is longer, with no plans to restart the therapy during trial participation.
5. Lung HRCT historically performed within 6 months prior to the Screening Visit and according to the minimum requirements for IPF diagnosis by central review based on subject's HRCT. If an evaluable HRCT is not available within 6 months prior to Screening, an HRCT will be performed at Screening to determine eligibility, according to the same requirements as the historical HRCT. The HRCT must demonstrate a usual interstitial pneumonia or probable usual interstitial pneumonia pattern based on central review vendor interpretation. Histopathology in combination with HRCT results supportive of an IPF or IPF likely diagnosis according to Raghu et al., 2022 can be submitted to support subject eligibility.
6. HRCT shows ≥10% to <50% parenchymal fibrosis (reticulation) and the extent of fibrotic changes is greater than the extent of emphysema on the most recent HRCT scan (central reviewer determined).
7. Meets all of the following criteria during the Screening Period, as determined by central review:
   a. FVC ≥45% predicted of normal
   b. forced expiratory volume in 1 second /FVC ≥0.7
   c. DLCO corrected for hemoglobin is ≥25% and ≤90% predicted of normal
8. Estimated minimum life expectancy of ≥30 months for non-IPF-related disease, in the opinion of the Investigator.
9. Vaccinations are up to date, according to the Investigator's discretion, given age, comorbidities, and local availability prior to trial drug dosing.
10. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

Exclusion Criteria:

Subjects will be ineligible for trial participation if they meet **any** of the following criteria:

1. Any of the following cardiovascular diseases:
   a. uncontrolled, severe hypertension (≥160/100 mmHg), within 6 months of Screening
   b. myocardial infarction within 6 months of Screening
   c. unstable cardiac angina within 6 months of Screening
2. Interstitial lung disease (ILD) associated with known primary diseases (e.g., sarcoidosis, amyloidosis, and coronavirus disease 2019 [COVID-19]), connective tissue disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjogren's, dermatomyositis, scleroderma), exposures (e.g., radiation, silica, asbestos, and coal dust) or drugs (e.g., amiodarone).
3. Known active bacterial, viral, fungal, mycobacterial, or other infection, including tuberculosis or atypical mycobacterial disease (fungal infections of nail beds are allowed). The subject must be 3 months beyond any acute infection with COVID-19 if there has been a prior infection.
4. Clinically significant pulmonary hypertension requiring chronic medical therapy.
5. Use of any of the following therapies within 4 weeks prior to Screening, during the Screening Period or planned during the trial: prednisone at steady dose >10 mg/day or equivalent or cyclosporine. Change in regimen or dosage of any immunosuppressant during the Screening Period through the end of trial participation will require consultation with and approval by the trial Medical Monitor. See Section 9.4.9 for full details. Avoiding the use of listed prohibited treatments must not be considered detrimental and must be

indicated by the treating physician. Subjects must not be withdrawn from any standard-of-care treatment that is considered necessary for the clinical management of the subject in order to fulfill the trial eligibility requirements.

6. Use of rifampin within 2 weeks prior to Day 1 or planned during the trial.
7. Malignant condition in the past 5 years (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
8. Women of childbearing potential (WOCBP) or male subjects not agreeing to use highly effective method(s) of birth control throughout the trial and for 4 weeks after last dose of trial drug. Females must refrain from egg/ova donation for 4 weeks after the last dose of trial drug and males must refrain from sperm donation for 3 months after the last dose of trial drug. Women are considered of childbearing potential if they are not postmenopausal and not surgically sterile (documented bilateral salpingectomy, bilateral oophorectomy, or hysterectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Fertile male subjects must use a condom throughout the trial and for 4 weeks after the last dose of trial drug. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
9. Pregnant or lactating women and women who plan to become pregnant or breast feed during the trial and within 4 weeks after the last dose of trial drug.
10. Current drug or alcohol abuse or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the subject.
11. Previous enrollment in this trial or participation in a prior fipaxalparant (HZN-825) or SAR100842 clinical trial.
12. Known history of positive test for human immunodeficiency virus (HIV). 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.
13. Active hepatitis (any of the following at Screening):

    Hepatitis B:
    - positive hepatitis B surface antigen
    - positive for anti-hepatitis B core antibody (anti-HBcAb) and a positive test for hepatitis B surface antibody (HBsAb) and presence of hepatitis B virus DNA
    - positive for HBcAb and a negative test for HBsAb and presence of hepatitis B virus DNA

    Hepatitis C:
    - positive anti-hepatitis C virus (anti-HCV) and positive HCV RNA.
14. Current alcoholic liver disease, primary biliary cirrhosis or primary sclerosing cholangitis.
15. Previous organ transplant (including allogeneic and autologous marrow transplant).
16. International Normalized Ratio (INR) >2, prolonged prothrombin time >1.5 × the upper limit of normal (ULN) or partial thromboplastin time >1.5 × ULN at Screening.
17. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 × ULN.
18. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 at Screening.
19. Total bilirubin >1.5 × ULN. Subjects with documented diagnosis of Gilbert's syndrome may be enrolled if their total bilirubin is ≤3.0 mg/dL.
20. Moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment according to the Child-Pugh scoring system.
21. Any confirmed Grade 3 or higher laboratory abnormality.
22. Any laboratory abnormality at Screening that, in the opinion of the Investigator, would preclude the subject's participation in the trial.
23. Exposure to an experimental drug or experimental vaccine within either 30 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is the longest, prior to Day 1.
24. Any other condition that, in the opinion of the Investigator, would preclude enrollment in the trial.

Eligibility Criteria for the Extension Phase:

Inclusion Criteria:

Eligible subjects must meet/provide **all** of the following criteria:

1. Written informed consent.
2. Completed the Double-blind Treatment Period (Week 52) of the Core Phase of the trial; subjects prematurely discontinued from trial drug in the Core Phase of the trial for reasons other than safety or tolerability may be included at the discretion of the Investigator after completing scheduled visits, including Week 52 assessments.
3. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the Extension Phase of the trial.

Exclusion Criteria:

Subjects will be ineligible for Extension Phase of the study if they meet **any** of the following criteria:

1. Anticipated use of another investigational agent for any condition during the course of the trial.
2. New diagnosis of malignant condition after enrolling in Trial HZNP-HZN-825-303 (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
3. Estimated minimum life expectancy ≤18 months, in the opinion of the Investigator.
4. WOCBP or male subjects not agreeing to use highly effective method(s) of birth control throughout the Extension Phase and for 4 weeks after last dose of fipaxalparant (HZN-825). Females must refrain from egg/ova donation for 4 weeks after the last dose of trial drug and males must refrain from sperm donation for 3 months after the last dose of trial drug. Women are considered of childbearing potential if they are not postmenopausal and not surgically sterile (documented bilateral salpingectomy, bilateral oophorectomy, or hysterectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
5. Pregnant or lactating women.
6. Any other new development of the disease/condition/significant laboratory test abnormality during the course of the Core Phase of the trial, in the opinion of the Investigator, that would potentially put the subject at unacceptable risk.
7. In the opinion of the Investigator, unlikely to comply with the trial protocol or has a concomitant disease or condition that could interfere with the conduct of the trial.

Dose Regimen/Route of Administration:

Core Phase: Subjects will take 2 tablets of trial drug orally in the morning and evening with a meal.

- Fipaxalparant (HZN-825) 300 mg QD regimen: 2 fipaxalparant (HZN-825) tablets in the morning and 2 placebo tablets in the evening.
- Fipaxalparant (HZN-825) 300 mg BID regimen: 2 fipaxalparant (HZN-825) tablets in the morning and 2 fipaxalparant (HZN-825) tablets in the evening.
- Placebo regimen: 2 placebo tablets in the morning and 2 placebo tablets in the evening.

Extension Phase: The dose regimen for all subjects will be fipaxalparant (HZN-825) 300 mg BID. Subjects will take 2 fipaxalparant (HZN-825) 150 mg tablets orally in the morning and evening with a meal. The dose for the Extension Phase may be modified based on the results of the Core Phase.

Dosage Form, Strength Formulation and Storage:

Fipaxalparant (HZN-825) 150 mg tablets and matching placebo tablets will be used in this trial. Fipaxalparant (HZN-825) 150 mg and placebo tablets will be packaged in blinded blister packs according to the dose regimens indicated (blister packs will be blinded for the Core Phase). The film-coated tablets are stored at controlled room temperature (20ºC to 25Cº, 68ºF to 77Fº).

Duration of Treatment and Follow-up:

The planned duration of the Double-blind Treatment Period of the Core Phase is 52 weeks. All subjects who complete the Double-blind Treatment Period may be eligible to enter into the Extension Phase of the trial and receive 52 weeks of open-label fipaxalparant (HZN-825). The total maximum exposure to trial drug during the trial is 104 weeks. Subjects not entering the Extension Phase of the trial will return to the clinic 4 weeks after the last dose of trial drug for a Safety Follow-up Visit.

Criteria for Evaluation:

Details of time points for trial activities and assessments are provided in Section 2.1 (Core Phase) and Section 2.2 (Extension Phase).

Efficacy will be assessed by FVC, 6MWT, PFS, patient-reported outcomes (K-BILD, L-IPF, LCQ, and SF-12), respiratory-related hospitalization, TOR, DLCO, IPF-related acute exacerbation, all-cause mortality, mortality due to respiratory deterioration, mortality due to IPF-related events and lung HRCT.

Blood samples for fipaxalparant (HZN-825) PK assessment, pharmacodynamic markers, and optional pharmacogenetic assessment (for drug metabolizing enzymes and/or transporters) will be collected.

Safety will be assessed via AEs, concomitant medication use, physical examinations, vital signs, orthostatic hypotension assessment, laboratory evaluations, 12-lead ECG, and echocardiogram.

Statistical Analyses:

Core Phase:

Primary Efficacy Endpoint

Change in FVC % predicted from Baseline to Week 52.

Key Secondary Efficacy Endpoint

Proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52.

Other Secondary Efficacy Endpoints

1. Change from Baseline in the 6MWT results to Week 52.
2. Change from Baseline in K-BILD scores to Week 52.
3. Change from Baseline in L-IPF scores to Week 52.
4. Change from Baseline in LCQ scores to Week 52.
5. Time to first hospitalization due to respiratory distress from Baseline up to Week 52.
6. Time to first onset of the composite endpoint of PFS from Baseline up to Week 52, where progression includes decline in FVC % predicted ≥10% or death.

Exploratory Endpoints

[redacted]

6. Time to death due to respiratory deterioration from Baseline up to Week 52.

[redacted]

[redacted]

Safety and Tolerability Endpoints

1. Incidence of TEAEs, SAEs and the AESI (orthostatic hypotension).
2. Concomitant medication use.
3. Vital signs.
4. 12-lead ECGs and echocardiograms.
5. Laboratory evaluations.

Pharmacokinetic Endpoint

Pre- and post-dose concentrations of fipaxalparant (HZN-825).

Statistical Analysis of Efficacy and Safety Endpoints

Efficacy analyses will be performed on the full analysis set (FAS), consisting of all subjects who are randomized to treatment and take at least 1 dose of trial drug; subjects will be analyzed according to the treatment group to which they were randomized. Safety analyses will be performed on the safety analysis set, consisting of all subjects who receive at least 1 dose or partial dose of trial drug.

Efficacy

The estimand for the primary efficacy analyses will be constructed to compare the primary endpoint between each dose regimen of fipaxalparant (HZN-825) and placebo using the treatment policy strategy approach to intercurrent events. All subjects who are randomized and take at least 1 dose of trial drug will be included in the primary efficacy analyses (FAS).

The primary efficacy endpoint will be change from Baseline in FVC % predicted to Week 52. A mixed model for repeated measures (MMRM) analysis of covariance model will be fit to the data using observed change in FVC % predicted values from all planned post-Baseline assessments (i.e., Weeks 4, 16, 28, 40, and 52) with covariates of stratification factors (concomitant use of IPF therapy [yes, no] and FVC % predicted at Baseline [≥70%, <70%]), treatment group, visit and visit-by-treatment group interaction. The unstructured variance-covariance matrix will be used in the model. Treatment group least squares means, associated standard error (SE) and their differences (each fipaxalparant [HZN-825] group minus placebo separately), SE of the difference, 90% confidence intervals (CIs) and p-value overall and for each visit will be provided.

For subjects with missing data at 1 or more time points, the available data will be included in the analysis.

One sensitivity analysis will consider whether data missing not at random may change the conclusion. A tipping point analysis will estimate the difference in true values among unobserved data that must occur to change the conclusion for each dose (i.e., change the result for each dose from $p \leq 0.10$ to $p > 0.10$). Intercurrent events will be addressed in the primary analysis by using treatment policy strategy with all available data. Sensitivity/supplemental analyses will assess the impact of missing data, as needed.

The key secondary endpoint will be the proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52 and will be analyzed using a logistic regression model with treatment group and stratified by factors used for stratifying the randomization. The logistic model will provide odds ratio, its 90% CI and p-value for comparing each fipaxalparant (HZN-825) group with the placebo group. Statistical significance for the key secondary endpoint will only be concluded if statistical significance is achieved for the primary efficacy endpoint.

[redacted] This analysis will have 2 potential outcomes:

- If neither dose regimen of fipaxalparant (HZN-825) shows better efficacy compared to placebo with an acceptable safety profile, the trial will be discontinued for futility.
- If 1 or both dose regimens of fipaxalparant (HZN-825) show better efficacy compared to placebo with an acceptable safety profile, the trial will continue with no changes.

The futility analysis will not be used to make a positive determination of efficacy to stop the trial.

Conditional power will be used to determine which of the options is chosen, with a conditional power of ≥10% required for at least 1 dose regimen to continue the trial. Other statistics, such as Bayesian statistics, may also be used for the futility analysis and dose selection.

To support the dose selection and as part of the Week 28 unblinded interim analysis, the FVC % predicted change from Baseline at Week 28 will be evaluated in subjects who were randomized with concomitant standard-of-care treatment at Baseline. Approximately 60 subjects in the standard-of-care stratum with 28 weeks of data (approximately 20 subjects per arm) will be included. The positive signal in the FVC % predicted change from Baseline at Week 28 and related results in standard-of-care subjects will support the dose selection and future trial design.

Additionally, safety will be assessed, and an fipaxalparant (HZN-825) dose regimen that has an unacceptable safety profile will be discontinued and subjects assigned to that dose regimen will be assigned to the other dose regimen for the remainder of the trial, if the other dose regimen continues.

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 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.

The overall statistical level is α=0.10 (2-sided). Because 2 dose regimens of fipaxalparant (HZN-825) will be compared to placebo, a hierarchical testing procedure will be used for multiple comparisons. Therefore, α=0.10 (2-sided) will be used in the final 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 fipaxalparant (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.

Safety and Tolerability

All subjects who receive at least 1 dose or partial dose of trial drug will be included in safety and tolerability analyses. Subjects who receive treatment other than that to which they were randomized will be included in summaries based on treatment received. Subjects who receive more than 1 treatment will be listed separately and included in summaries with the treatment received most frequently.

Safety analyses will be summarized by treatment group. The incidence of TEAEs, treatment-related TEAEs, TEAEs Grade 3 and above, AESI, SAEs, and TEAEs leading to trial drug discontinuation by Preferred Term and System Organ Class will be summarized. AE rates (events per patient-year of follow-up during the Double-blind Treatment Period) will also be summarized to account for different treatment durations. Orthostatic hypotension is prospectively defined as an AESI and will be summarized separately.

Summary statistics will be used for laboratory values, vital signs, ECG results, and use of concomitant medications.

Statistical Analyses:

Extension Phase:

Primary Efficacy Endpoint

Change from both Baselines in FVC % predicted at Week 104.

Safety and Tolerability Endpoints

- Incidence of TEAEs and the AESI (orthostatic hypotension) in the Extension Phase.
- Concomitant medication use in the Extension Phase
- Change from OLE Baseline in vital signs in the Extension Phase
- Change from OLE Baseline in 12-lead ECG measurements in the Extension Phase
- Change from OLE Baseline in clinical safety laboratory test results in the Extension Phase

Exploratory Endpoints

- Change from both Baselines in proportion of subjects with decline in FVC % predicted ≥10% at Week 52 of the Extension Phase (Trial Week 104).
- Change from both Baselines in the 6MWT results to Week 104
- Change from both Baselines in K-BILD scores to Week 104
- Change from both Baselines in L-IPF scores to Week 104
- Change from both Baselines in LCQ scores to Week 104
- [redacted]
- [redacted]
- Time to first onset of the composite endpoint of PFS from fipaxalparant (HZN-825) Baseline up to Week 104, where progression includes decline in FVC % predicted ≥10% from Baseline or death
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Time to death due to respiratory deterioration from fipaxalparant (HZN-825) Baseline up to Week 104
- [redacted]
- [redacted]

Exploratory PK Endpoints

- Pre- and post-dose concentrations of fipaxalparant (HZN-825) in the Extension Phase

Statistical Analysis of Efficacy and Safety Endpoints

Efficacy analyses will be performed on the FAS, consisting of all subjects who entered and received at least 1 dose or partial dose of fipaxalparant (HZN-825) in the Extension Phase. Subjects will be analyzed according to the treatment group to which they were randomized in the Core Phase and combined into an 'overall' group.

Safety analyses will be performed on the safety analysis set, consisting of all subjects who receive at least 1 dose or partial dose of fipaxalparant (HZN-825) in the Extension Phase. This analysis set will be analyzed according to the group determined by the treatment the subject received in the Core Phase and combined into an 'overall' group.

All efficacy and safety endpoints will be summarized using descriptive statistics.

Sample Size Estimate:

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 fipaxalparant (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.

2.1 Schedule of Assessments During the Core Phase

	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 use history		X	X												
Weight		X	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	
Titrated oxygen requirement			X					X		X		X		X	
6MWT			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
Physical examination [15]		X	X							X				X	X
Vital signs, including pulse oximetry [16]		X	X		X		X	X	X	X	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** 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)**
Orthostatic hypotension assessment			X		X					X				X	
12-lead electrocardiogram [17]		X	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	X
Fasting glucose and lipids [20]			X							X				X	
hsCRP			X							X				X	
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	
Pharmacodynamic serum sample (collect pre-dose) [25]			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; LCQ=Leicester Cough Questionnaire; L-IPF=Living with IPF; K-BILD= King's Brief Interstitial Lung Disease Questionnaire; $LPAR_1$=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 **OLE** 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 fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (HZN-825) 300 mg BID, or placebo.
12. For subjects who are entering the OLE 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 Section 9.5.5.9 for details.
19. For subjects taking warfarin, physicians should monitor their INR, 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 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 $LPAR_1$ 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 fipaxalparant (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.

2.2 Schedule of Assessments During the Extension Phase

	Open-label Treatment Period										Safety Follow-up Visit
Trial Visit	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**4 weeks after last dose of fipaxalparant (HZN-825) 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	
Fipaxalparant (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

	Open-label Treatment Period										Safety Follow-up Visit
Trial Visit	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**4 weeks after last dose of fipaxalparant (HZN-825) 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)**
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	
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; 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; SF-12=SF-12® Health Survey; W=Week; WOCBP=women of childbearing potential

1. Subjects will receive the first dose of open-label fipaxalparant (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 fipaxalparant (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 fipaxalparant (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 fipaxalparant (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 is required for Week 80 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 fipaxalparant (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 fipaxalparant (HZN-825) is administered in the clinic.
13. See Section 9.5.5.9 for details. Samples collected at the Week 52 Visit should be collected before the first dose of open-label fipaxalparant (HZN-825) is administered in the clinic.
14. For subjects taking warfarin, physicians should monitor their **INR**, as needed.

15. Includes fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides.
16. See 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 fipaxalparant (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 Table 9.1 for restrictions regarding medications.

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	6-Minute Walk Test
AE	adverse event
AESI	adverse event of special interest
ALAT	Latin American Thoracic Society
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
ATX	autotaxin
AUC	area under the (plasma) concentration-time curve
AUC	area under the concentration-time curve from 0 to 12 hours
BAL	bronchoalveolar lavage
BID	twice daily
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
C_{trough}	minimum total trough concentration
CYP	cytochrome P450
DLCO	diffusing capacity of the lungs for carbon monoxide
DOCA	deoxycorticosterone acetate
DSUR	Development Safety Update Report
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ERS	European Respiratory Society
EU	European Union
EU CT	European Union Clinical Trials
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FVC	forced vital capacity

Abbreviation	Definition
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HCV	hepatitis C virus
HRCT	high-resolution computed tomography
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
IDMC	independent data monitoring committee
ILD	interstitial lung disease
IND	Investigational New Drug
IPF	idiopathic pulmonary fibrosis
IRT	interactive response technology
JRS	Japanese Respiratory Society
K-BILD	King's Brief Interstitial Lung Disease Questionnaire
LCQ	Leicester Cough Questionnaire
L-IPF	Living with IPF
LPA	lysophosphatidic acid
$LPAR_1$	lysophosphatidic acid receptor 1
MMRM	mixed model for repeated measures
mRSS	modified Rodnan skin score
OAT	organic anion transporter
OLE	open-label extension
PFS	progression-free survival
PK	pharmacokinetic
QD	once daily
SAE	serious adverse event
SE	standard error
SF-12	SF-12® Health Survey
SLCO	solute carrier organic anion transporter family member
SOC	System Organ Class

Abbreviation	Definition
$S_{p,O2}$	oxygen saturation
SSc	systemic sclerosis
TEAE	treatment-emergent adverse event
TOR	titrated oxygen requirement
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

Abbreviations that appear only in figures and tables or in a single paragraph are defined with the relevant figures, tables and paragraphs.

5 ETHICS

5.1 Institutional Review Board/Independent Ethics Committee

The Principal Investigator (Investigator), the Sponsor and/or contract research organization authorized by the Sponsor will submit this protocol, any protocol modifications, the informed consent form (ICF) and all applicable trial documentation to be used in this trial to the appropriate external review bodies for review and approval/favorable opinion. A letter confirming the external review bodies' approval/favorable opinion of the protocol, the subject ICF and applicable trial documentation, a list of the external review bodies' members involved in the vote, as well as a statement that the external review body is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations, must be forwarded to the Sponsor or its designee **prior to** the enrollment of subjects into the trial. A copy of the approved ICF will also be forwarded to the Sponsor or its designee. Appropriate reports on the progress of the trial will be made to the external review bodies and the Sponsor or its designee by the Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

5.2 Ethical Conduct of the Trial

The Investigators will ensure that this trial is conducted in a manner that fully conforms with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The trial must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Tripartite Guideline or with local law if it affords greater protection to the subject. For trials conducted in the United States (US) or under a US Investigational New Drug (IND) program, the Investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations (CFR), subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects" and part 56, "Institutional Review Boards."

5.3 Subject Information and Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations) to obtain signed informed consent from each subject prior to participating in this trial after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial. Both the Core Phase and the optional open-label extension (OLE) Phase will require separate ICFs to be signed by subjects.

The Investigator or designee must also explain that the subjects are completely free to refuse to enter the trial or to withdraw from it at any time, for any reason.

The ICF and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written ICF. The Investigator will inform the subject of changes in a

timely manner and will ask the subject to confirm his/her participation in the trial by signing the revised ICF. Any revised written ICF and written information must receive the external review bodies' approval/favorable opinion in advance of use.

All signed ICFs are to remain in the Investigator's site file or, if locally required, in the subjects' notes/files of the medical institution.

The electronic case report forms (eCRFs) for this trial contain a section for documenting all subject informed consent(s) and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the ICF should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the trial.

5.4 Compensation for Health Damage of Subjects/Insurance

The Sponsor maintains clinical trial insurance coverage for this trial in accordance with the laws and regulations of the country in which the trial is performed.

5.5 Confidentiality

All records identifying the subject will be kept confidential and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the eCRF and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Trial findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the Sponsor, external review bodies, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the trial are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects to be identified.

6 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

The Sponsor of this trial is Horizon Therapeutics Ireland DAC (Horizon, a wholly owned subsidiary of Amgen Inc.). Horizon and/or designee personnel will serve as the Medical Monitor (see Section 17.1 for details). The Sponsor will be responsible for timely reporting of serious adverse events (SAEs) to regulatory authorities as required. The Sponsor will be responsible for timely reporting of SAEs and any other new pertinent safety information to all Investigators as required.

The trial will be conducted at approximately 85 trial sites in North America, Europe, South America, Africa, Asia (including Japan), and Australia. Prior to initiation of the trial, each Principal Investigator in the US will provide the Sponsor or its designee with a fully executed and signed Food and Drug Administration (FDA) Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms will also be completed by all Sub-Investigators listed on Form 1572. It is the responsibility of the Investigators or Sub-Investigators to advise the Sponsor of any change in the relevant financial interests that occur during the trial and the 1-year period following its completion.

Table 6.1 lists other organizations that are critical to the conduct of the trial, with a brief description of their roles:

Table 6.1 Table of Non-Sponsor Trial Responsibilities

Trial Responsibility	Organization
Contract research organization	PPD (subsidiary of Thermo Fisher Scientific) Biotech 929 North Front Street Wilmington, NC 28401
Central safety laboratory	PPD Laboratories – North and South America 2 Tesseneer Drive Highland Heights, KY 41076 PPD Laboratories – Middle East and Africa Clusterpark, Kleine Kloosterstraat 19 1932 Zaventem, Belgium PPD Laboratories – Asia Pacific 61, Science Park Road #02-11/14, The Galen, Singapore Science Park II Singapore 117525

7 INTRODUCTION

7.1 Background

7.1.1 Idiopathic Pulmonary Fibrosis

The interstitial lung diseases (ILDs) are a heterogeneous group of parenchymal lung diseases characterized by both fibrosis and inflammation. The etiology of ILDs involve known causes, such as autoimmune connective tissue disease, hypersensitivity to inhaled organic antigens, drug exposure or sarcoidosis, while the idiopathic interstitial pneumonias have no identifiable cause [International consensus statement, 2000]. Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause and is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia in the lungs.

In 2018, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and the Latin American Thoracic Society (ALAT) jointly updated recommendations to reach a consensus for the diagnosis of IPF and provided additional updates to the guidance in 2022 [Raghu et al., 2018; Raghu et al., 2022]. IPF is one of the most common types of ILD, estimated to affect 132,000 to 200,000 people in the US. In the US, approximately 50,000 new cases are diagnosed each year, and as many as 40,000 patients die from IPF each year according to the Pulmonary Fibrosis Foundation. IPF is diagnosed more frequently in men than women, usually occurs in adults over 50 years of age and is characterized by progressive dyspnea, non-productive cough and progressive pulmonary insufficiency consistent with increasing fibrosis.

The reported incidence rates of IPF vary considerably, which is likely due to differences between diagnostic approaches and definitions used for IPF. A systematic review of the global incidence of IPF estimated a rate of 2.8 to 9.3 per 100,000 per year in North America and Europe [Barratt et al., 2018]. Regional variation within countries has also been observed, possibly reflecting exposure to environmental or occupational risk factors [Gribbin et al., 2006; Navaratnam et al., 2011; Raghu et al., 2014; Hopkins et al., 2016; Strongman et al., 2018]. Evidence suggests that the incidence of IPF is rising [Hutchinson et al., 2015]. A recent analysis of a United Kingdom-based, primary care database calculated a rise in incidence of 78% between 2000 and 2012, as well as a doubling of prevalence, estimated at 38.8 per 100,000 [Strongman et al., 2018], with the consequential growing economic burden on global health care [Diamantopoulos et al., 2018]. Mortality following diagnosis of IPF is high, with a median survival of 2 to 3 years from time of diagnosis [Raghu et al., 2011].

The antifibrotic drugs nintedanib and pirfenidone were first approved in 2014 by the US FDA. Nintedanib and pirfenidone are approved for the treatment of IPF and nintedanib is also approved for treatment of chronic fibrosing ILDs with a progressive phenotype and slowing the rate of decline in pulmonary function in patients with systemic sclerosis (SSc)-associated ILD [OFEV™ Full Prescribing Information; ESBRIET™ Full Prescribing Information]. Nintedanib has also been approved in multiple regions and countries, including Europe, Canada, Japan, and Brazil. Pirfenidone has also been approved in multiple regions and countries, including Europe, Canada, Japan, Brazil, Norway, Iceland, India, South Korea, Argentina, and Mexico.

Important warnings and precautions for use of nintedanib and pirfenidone include elevated liver enzymes and drug-induced liver injury as well as gastrointestinal disorders. Although these treatments offer substantial improvement over previously available therapy options, additional opportunities remain for novel or add-on treatments that will further arrest disease progression and potentially improve lung function over time.

7.1.2 Lysophosphatidic Acid Receptor 1 ($LPAR_1$) and Related Mechanism

The signal transduction cascades initiated by lysophosphatidic acid (LPA) (1-oleoyl-sn-glycerol 3-phosphate and derivatives) binding to LPA receptor 1 ($LPAR_1$) are of interest in the therapeutic treatment of a several diseases due to involvement of the $LPAR_1$ pathway in inflammation and fibrosis. Extracellularly, LPA can be produced by 2 different mechanisms from phospholipids. Autotaxin (ATX) is the enzyme that generates the majority of serum LPA. There is also an ATX-independent mechanism whereby LPA is generated from phospholipids via a 2-step process. Phospholipase D1 or phospholipase D2 converts phospholipids to phosphatidic acid, which is then converted to LPA by phospholipase A1 or phospholipase A2 [Geraldo et al., 2021]. Below is a review of the background of ATX, LPA and $LPAR_1$, as well as the key information linking their activities to diseases characterized by inflammation and fibrosis.

7.1.2.1 Autotaxin

ATX is an ecto-enzyme that hydrolyzes the phosphodiester bonds in lysophospholipids ultimately leading to the production of LPA [Knowlden and Georas, 2014; Valdes-Rives and González-Arenas, 2017]. ATX is thought to be the primary enzyme responsible for the production of LPA, the ligand for the LPAR family of receptors, including $LPAR_1$, in serum [Nakanaga et al., 2010; Knowlden and Georas, 2014]. The evidence for this includes: 1) levels of LPA and ATX correlate in human serum samples, 2) mice heterozygous for ATX showed ~50% reduction in LPA levels, 3) depletion of ATX from serum abrogates lysophospholipidase activity and LPA levels are non-detectable, and 4) administration of an ATX inhibitor to healthy humans in a clinical trial resulted in human decreases of serum LPA levels by ~80% [Tanaka et al., 2006; Tsuda et al., 2006; van Meeteren et al., 2006; Nakamura et al., 2008; Maher et al., 2018; van der Aar et al., 2020].

Inhibition of ATX has been evaluated in a mouse model of lung fibrosis induced by administration of bleomycin, with conflicting results regarding efficacy. Several studies have demonstrated that blockade of the ATX enzyme leads to reduction in LPA levels, histological disease score of lung and/or lung collagen levels [Oikonomou et al., 2012; Desroy et al., 2017; van der Aar et al., 2020]. Additionally, deletion of ATX in the bronchial epithelial cells or macrophages in mice reduces pulmonary fibrosis-induced by bleomycin [Oikonomou et al., 2012]. However, there is also evidence that the LPA species induced in lungs by bleomycin in the mouse model is produced by an ATX-independent mechanism [Black et al., 2016]. Further, inhibition with a specific inhibitor of ATX led to reduction in ATX activity systemically and in the lung of mice with pulmonary fibrosis induced by bleomycin without reduction in pulmonary LPA levels or fibrosis, suggesting the ATX-independent mechanisms were responsible for local generation of LPA in the injury lung [Black et al., 2016]. In a mouse model of smoke inhalation, ATX inhibition reduced immune cell infiltration into the

bronchoalveolar lavage (BAL) fluid and lung gene expression of tobacco smoke-induced genes [Blanqué et al., 2015].

Immunohistochemistry analysis of lung tissue isolated from patients with ILDs, including IPF, interstitial pneumonia and the fibrosing form of nonspecific interstitial pneumonia, showed increased protein levels of ATX levels in patients with IPF and fibrotic nonspecific interstitial pneumonia [Oikonomou et al., 2012].

In summary, ATX is upregulated in several forms of fibrosing ILDs, but animal data show fibrosis induced by bleomycin in lungs of mice might be through an ATX-independent mechanism and that inhibition of ATX might not be effective in lung fibrosis. LPA signals through at least 6 type I rhodopsin-like receptors (LPARs) that exhibit widespread, but differential, tissue distribution, as well as overlapping specificities [Yung et al., 2014]. LPARs couple with G-proteins, crucial molecular switches activating numerous signal transduction pathways [Oldham and Hamm, 2008]. Overall, any LPA effect in each cell type depends on its local concentration, regulated by both ATX-dependent and -independent pathways, the levels of possible agonists and antagonists and the relative abundance of the different receptor subtypes [Ninou et al., 2018]. These complexities associated with ATX inhibition as a potential therapeutic approach are distinct from the mechanism of action of fipaxalparant (HZN-825), which acts as a selective, small molecule antagonist of $LPAR_1$ that antagonizes the pathway of LPA production. Fipaxalparant (HZN-825) will inhibit LPA produced by ATX-dependent and -independent pathways from signaling through $LPAR_1$ (see Sections 7.1.2.3 and 7.1.3).

7.1.2.2 Lysophosphatidic Acid

LPA is a small bioactive glycerophospholipid present in all eukaryotic tissues and produced from membrane phospholipids via different enzymatic pathways. LPA is also generated at sites of inflammation or cell injury [Zhao and Natarajan, 2013]. LPA accumulates in the serum of patients with SSc, in BAL fluid of patients suffering from IPF and in human atherosclerotic plaques [Tager et al., 2008; Tokumura et al., 2009; Schober and Siess, 2012].

LPA can activate 6 distinct G protein-coupled receptors that differ in their tissue distribution and coupling to downstream signaling pathways enabling LPA to elicit a variety of cellular responses including mitogenic effects, differentiation, survival, cytoskeletal reorganization, and cell migration [Fukushima et al., 2001; Chun et al., 2002; Takuma et al., 2002]. LPA has been shown to promote the differentiation, proliferation and migration of cells from a mesenchymal origin, including lung and dermal fibroblasts, and also induce the de-differentiation of vascular smooth muscle cells [Kim et al., 2006; Yin et al., 2008].

LPA has direct effects on inflammatory cells of both the innate and adaptive immune systems including being a powerful stimulator of human neutrophil motility, causing an increase in binding of monocytes and neutrophils to human aortic endothelial cells, activating human eosinophils. The effects on eosinophils are mediated by $LPAR_1$ and/or $LPAR_3$ as they are antagonized by an $LPAR_1$/$LPAR_3$ antagonist [Idzko et al., 2004]. LPA increases the allostimulatory function of mature dendritic cells, inhibits their capacity to induce T helper 1 cell differentiation and increases the ability of dendritic cells to polarize T cells to a Th2 phenotype [Panther et al., 2002].

7.1.2.3 Lysophosphatidic Acid Receptor 1

In nonclinical studies, $LPAR_1$ antagonism decreased organ fibrosis in several experimental settings, including models of skin [Cabello-Verrugio et al., 2011], lung [Tager et al., 2008] and kidney [Pradère et al., 2007] fibrosis. $LPAR_1$ knockout mice were also protected from developing skin and lung fibrosis [Tager et al., 2008; Cabello-Verrugio et al., 2011]. Additionally, LPA-induced cardiac fibroblast proliferation and extracellular matrix production are mediated by $LPAR_1$ [Cabello-Verrugio et al., 2011]. $LPAR_1$ has also been implicated in the development of IPF given its role in mediation of fibroblast recruitment, differentiation of cells into myofibroblasts, inflammation, extracellular matrix deposition, vascular leak, and endothelial barrier dysfunction in animal models [Tager et al., 2008; Ninou et al., 2018; Swaney et al., 2010]. In the bleomycin mouse model of pulmonary fibrosis, $LPAR_1$-deficient mice showed reduced levels of fibroblast recruitment and decreased vascular permeability, indicating a protective role for decreased LPA signaling. Additionally, $LPAR_1$ knockout mice showed reduction in bronchial epithelial cells apoptosis following bleomycin administration [Funke et al., 2012].

$LPAR_1$ receptor antagonism has also been shown to block LPA induced differentiation of bone marrow-derived mesenchymal stem cells into myofibroblasts and LPA-induced proliferation of normal human lung fibroblasts [Tang et al., 2014; Qian et al., 2012]. LPA signaling through $LPAR_1$ promoted the resistance of lung fibroblasts to apoptosis, which has also been implicated in IPF [Funke et al., 2012].

In a Phase 2 clinical trial of IPF, $LPAR_1$ antagonism significantly slowed the rate of decline in forced vital capacity (FVC) compared with placebo [Palmer et al., 2018]. These findings suggest a role for antagonists of $LPAR_1$ as therapeutic treatments for a variety of fibrotic conditions.

7.1.3 Fipaxalparant (HZN-825)

7.1.3.1 Pharmacology Related to Potential Therapeutic Activity

The activity of fipaxalparant (HZN-825), an $LPAR_1$-specific antagonist, was evaluated in vitro in lung fibroblasts isolated from patients with IPF and in dermal fibroblasts isolated from patients with SSc. LPA-induced signaling in IPF or diffuse cutaneous SSc patient-derived fibroblasts was blocked by fipaxalparant (HZN-825) in a concentration-dependent manner, confirming that LPA signaling in these cells is a result of $LPAR_1$ [Ledein et al., 2020]. Fipaxalparant (HZN-825) was also able to block LPA-induced differentiation of IPF patient-derived fibroblasts into myofibroblasts in a dose-dependent manner, reduced the secretion of inflammatory markers and activated Wnt family members [Ledein et al., 2020].

The activity of fipaxalparant (HZN-825) was also evaluated in vivo in models of skin, kidney and heart fibrosis. Two models of dermal fibrosis were used to evaluate the effect of fipaxalparant (HZN-825) treatment in comparison with the positive control Gleevec® (imatinib mesylate). In a mouse model of bleomycin-induced skin fibrosis, therapeutic dosing of fipaxalparant (HZN-825) prevented progression of fibrosis, as indicated by reductions in dermal thickness, myofibroblast numbers, and hydroxyproline content of the bleomycin-injected skin. Treatment of tight-skin 1 (Tsk-1) mice with fipaxalparant (HZN-825) prevented the progression of skin fibrosis, with significant reductions in hypodermal thickness, myofibroblast numbers and hydroxyproline content; the anti-fibrotic effects were comparable to those of imatinib.

The role of LPA and $LPAR_1$ signaling was also evaluated in an experimental model of lung irritation to study the impact on inflammation that can lead to airway remodeling (Study report GVV0148). Fipaxalparant (HZN-825) dose dependently reduced the total cells and eosinophils in the BAL fluid, with 91% reduction in total cellularity of BAL and 99% reduction in eosinophil number at 24 hours.

In addition, fipaxalparant (HZN-825) treatment improved kidney function in models of hypertension- or nephrotoxicity-induced renal injury and showed beneficial effects on cardiac function and hypertrophy in models of hypertension or diabetes-related cardiac injury, fibrosis and heart failure. In parallel, fipaxalparant (HZN-825) showed moderate but significant antithrombotic activity in acute models of coagulation and arterial thrombosis.

7.1.3.2 Nonclinical Safety

In animal studies, single oral administration of fipaxalparant (HZN-825) at up to 2000 mg/kg to rats and up to 1000 mg/kg to dogs resulted in no adverse findings in safety pharmacology and single-dose toxicity studies. The no-observed-adverse-effect level values in the 6-month rat and 9-month dog toxicology studies were 2000 and 1000 mg/kg/day, respectively, which were the highest dose levels evaluated in each species. Fipaxalparant (HZN-825) and M4 were neither mutagenic nor clastogenic/aneugenic in a standard battery of genetic toxicology studies. No compound-related effects on fertility and/or early embryonic development were noted in either male or female rats administered fipaxalparant (HZN-825) at dosages up to 2000 mg/kg/day. There was no evidence of developmental toxicity in embryo-fetal toxicity studies conducted in both rats and rabbits at dose levels up to 2000 mg/kg/day. Additional information regarding the nonclinical safety pharmacology studies is provided in the current version of the Investigator's Brochure.

7.1.3.3 Nonclinical Pharmacokinetics

Following single oral administration of [^{14}C]-fipaxalparant (HZN-825) to rats, maximum observed concentration (C_{max}) was observed at 1 to 2 hours post dose and oral bioavailability was estimated to be 17.8%. In general, increases in exposure were less than dose-proportional in both species, and negligible accumulation in C_{max} or area under the plasma concentration-time curve (AUC) was observed after repeated dosing. Plasma elimination half-lives in rats, rabbits, and dogs ranged from 1.4 to 3.6 hours and plasma clearance was 0.226 to 1.46 L/h/kg. The excretion of [^{14}C]-fipaxalparant (HZN-825) and/or its metabolites in rats and dogs occurred almost exclusively via feces, regardless of the route of administration. The main in vitro metabolic pathways of [^{14}C]-fipaxalparant (HZN-825) were identified as single hydroxylation followed by glucuronidation and direct acylglucuronidation of parent drug. After oral administration of [^{14}C]-fipaxalparant (HZN-825) to rats, unchanged fipaxalparant (HZN-825) was found to be the predominant peak in plasma, amounting to 80% to 89% of total radioactivity in plasma.

In protein binding studies, [^{14}C]-fipaxalparant (HZN-825) was found to be highly protein bound in all species, with fraction bound ranging from 98.94% to 99.97%. Human serum albumin was found to be the major binding protein in human plasma. Additional information regarding the

nonclinical pharmacokinetics (PK) studies is provided in the current version of the Investigator's Brochure.

7.1.3.4 Clinical Experience

Fipaxalparant (HZN-825) has been administered to 244 healthy subjects in nine Phase 1 completed clinical trials and 31 subjects with diffuse cutaneous SSc in a Phase 2a clinical trial. In clinical trials completed, as provided in the current version of the Investigator's Brochure, fipaxalparant (HZN-825) was well-tolerated and showed similar safety and pharmacokinetic profiles across healthy subjects (including elderly healthy subjects) and subjects with diffuse cutaneous SSc. In the Phase 2a trial, treatment with fipaxalparant (HZN-825) 300 mg twice daily (BID) resulted in numerical improvement from baseline compared with placebo at the end of the 8-week double-blind period and at the end of the 16-week, open-label period based on clinical outcomes, including the modified Rodnan skin score (mRSS), Health Assessment Questionnaire – Disability Index (HAQ-DI) and other components of the Scleroderma Health Assessment Questionnaire, overall disease severity and pruritus [Allanore et al., 2018].

In Phase 1 Trial HZNP-HZN-825-104 in healthy subjects, preliminary data suggested there are no relevant mutual drug-drug interactions between fipaxalparant (HZN-825) and pirfenidone/nintedanib at clinical doses. The 90% confidence interval (CI) of the geometric least squares mean ratio for both AUC and C_{max} (test vs reference) was within the predefined no-effect bound of (0.70, 1.43).

No SAEs or severe adverse events (AEs) occurred in Phase 1 trials. One subject experienced AEs leading to permanent trial drug discontinuation (*Nausea* and *Abdominal pain*) on fipaxalparant (HZN-825) 300 mg BID and midazolam. In the Phase 2a trial, fipaxalparant (HZN-825) 300 mg BID given up to 24 weeks was well-tolerated. During the 8-week double-blind period, the most frequent treatment-emergent adverse events (TEAEs) in the fipaxalparant (HZN-825) group were headache, diarrhea, nausea and fall.

Based on safety results to date, orthostatic hypotension is identified as a potential risk of fipaxalparant (HZN-825) therapy that will continue to be monitored as an AE of special interest (AESI) (Section 9.5.5.1.1.4). Additionally, increases in hepatic transaminases have been seen in blinded clinical studies with fipaxalparant (HZN-825). These events are mostly non-serious and reversible. Liver enzyme elevation will be monitored per FDA guidelines (Section 9.3.3.1)

Additional and current information regarding the safety of fipaxalparant (HZN-825) is provided in the current Investigator's Brochure.

7.1.3.5 Benefit/Risk Assessment

Fipaxalparant (HZN-825) is a new therapeutic agent under development for treating fibrotic diseases, including SSc. The anti-inflammatory and anti-fibrotic properties of $LPAR_1$ antagonism have been demonstrated in both animal models and in a Phase 2 clinical trial. Positive changes in mRSS, HAQ-DI and $LPAR_1$ pathway genes were detected in the completed Phase 2a trial in diffuse cutaneous SSc. Results of trials to date support the safety and potential

efficacy of 300 mg BID for up to 24 weeks of treatment. The exposure, PK and safety profiles of fipaxalparant (HZN-825) were similar across the completed trials.

Based on the cumulative safety data available to date on fipaxalparant (HZN-825), transaminase increase has been evaluated as an important identified risk and orthostatic hypotension, drug-drug interactions, and embryo-fetal toxicity are considered as important potential risks. No severe AEs or SAEs were reported in healthy subjects in Phase 1 trials. TEAEs of orthostatic hypotension, postural dizziness, flatulence, and abdominal pain were slightly more frequent in fipaxalparant (HZN-825)-treated than in placebo-treated subjects. Orthostatic hypotension was mainly observed in healthy subjects and tended to be less marked in subjects with diffuse cutaneous SSc treated with fipaxalparant (HZN-825). The potential safety risk of fipaxalparant (HZN-825) due to drug-drug interactions is considered low as medications that may have potential interactions with fipaxalparant (HZN-825) are restricted in this protocol (Section 9.4.9).

Participants with IPF receiving fipaxalparant (HZN-825) may benefit from the $LPAR_1$ antagonism by slowing the decline of lung function due to progressive fibrotic disease. Subjects in the trial will also benefit from receiving trial-related medical examinations, imaging and laboratory tests at no cost.

AESIs are considered monitorable. Taking into account mitigation measures to minimize risk to subjects in this trial, the potential risks identified in association with fipaxalparant (HZN-825) treatment and the trial as a whole are justified by the anticipated benefits that may be afforded to patients with IPF.

Additional information regarding the benefit and risks of fipaxalparant (HZN-825) are located in the current Investigator's Brochure Section 6.2 and Section 12.

7.2 Rationale for this Trial

IPF is an advancing and fatal lung disease with significant morbidity and reported increasing incidence and prevalence. Pirfenidone and nintedanib were approved by the FDA in 2014 for the treatment of IPF based on positive results in Phase 3 trials, and both of these antifibrotic drugs are conditionally recommended in the 2015 ATS/ERS/JRS/ALAT Clinical Practice Guideline [Raghu et al., 2015]. Although an improvement over previously suggested therapies, their capacity to reduce but not completely arrest progression of lung fibrosis or improve lung function over time presents an opportunity for novel or add-on pharmacologic agents.

Pirfenidone should be taken 3 times daily with food at a target dose that is generally achieved over 14 days [Lancaster et al., 2017]. Nintedanib recommended dosage includes BID dosing with food. In randomized, double-blind, placebo-controlled trials, gastrointestinal adverse reactions occurring in ≥10% of treated subjects that may require temporary dosage reductions or discontinuations for pirfenidone and nintedanib included diarrhea, nausea, abdominal pain, and vomiting [ESBRIET Full Prescribing Information; OFEV Full Prescribing Information]. While significant advances have been made in the past decade using pharmacological therapy, there remains a substantial unmet clinical need for treatment regimens with improved efficacy, tolerability and dosing convenience for patients with IPF.

Fipaxalparant (HZN-825) is under investigation as a novel therapy for IPF because it selectively antagonizes $LPAR_1$, which has been shown to be associated with skin, pulmonary, cardiac, peritoneal, and tubulointerstitial fibrosis and has potential as a new therapeutic for treating fibrotic diseases, including IPF. Details are provided in the current version of the Investigator's Brochure.

This trial is designed to evaluate the efficacy and safety of fipaxalparant (HZN-825) in subjects with IPF. The trial will be conducted in 2 parts, Part 1 (Core Phase) and Part 2 (Extension Phase). In the Core Phase of the trial, subjects will receive fipaxalparant (HZN-825) 300 mg once daily (QD), fipaxalparant (HZN-825) 300 mg BID, or placebo during the 52-week Double-blind Treatment Period. Subjects who complete the Double-blind Treatment Period (Week 52) in the Core Phase may be eligible for the Extension Phase and will receive open-label fipaxalparant (HZN-825) 300 mg BID for 52 weeks (up to Week 104). This Extension Phase will allow subjects to have up to 24 months of treatment with fipaxalparant (HZN-825), as well as limit the duration subjects are exposed to placebo. The trial is designed with the Extension Phase to allow examination of long-term safety and tolerability of fipaxalparant (HZN-825), assessment of the durability of response and/or improved response in subjects who received fipaxalparant (HZN-825) in the Core Phase and evaluation of efficacy in subjects who received placebo in the Core Phase.

7.3 Rationale for Dose Selection

The dose regimens to be evaluated in this trial are 300 mg QD and 300 mg BID with a meal using fipaxalparant (HZN-825) tablets manufactured by [redacted]. These regimens are selected based on a comprehensive review of preclinical data assessing in vitro $LPAR_1$ inhibitory activity, information from rodent fibrosis models, Phase 1 PK data and information from a Phase 2a trial in subjects with diffuse cutaneous SSc.

The completed Phase 2a trial in diffuse cutaneous SSc supports the safety and potential efficacy of 300 mg BID for up to 24 weeks of treatment. The exposures and safety profiles of fipaxalparant (HZN-825) in this trial were similar to those previously observed in healthy subjects, and positive changes in mRSS, HAQ-DI and $LPAR_1$ pathway genes were detected. [redacted] in the Phase 2a trial is thus considered a relevant target exposure of fipaxalparant (HZN-825) for IPF, as by blocking $LPAR_1$ signaling, fipaxalparant (HZN-825) has the potential to specifically and efficaciously resolve the underlying pathologies of IPF, thereby reducing the severity and progression of the disease.

Preclinical data also support the fipaxalparant (HZN-825) exposures targeted for this trial. The minimum total C_{trough} in humans needed for inhibition of $LPAR_1$ activity was between 25.3 ng/mL and 1536 ng/mL based on in vitro potency evaluations. The half-maximal inhibitory concentration (IC_{50}) of fipaxalparant (HZN-825) against $LPAR_1$ activity ranged from 1.1 ng/mL to 66.8 ng/mL without presence of albumin, corresponding to 25.3 ng/mL to 1536 ng/mL after adjusting for the 23-fold shift in IC_{50} in the presence of 3.5% albumin in the range of human plasma albumin level of 3.5 g/dL to 4.5 g/dL [Human Albumin, 2009]. In a rat deoxycorticosterone acetate (DOCA) salt model, fipaxalparant (HZN-825) reduced cardiac

hypertrophy, hydroxyproline levels, and kidney damage at 10 mg/kg BID, with a steady-state area under the concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) of 12000 ng*h/mL.

Based on preliminary PK results from Trial HZNP-HZN-825-101, 300 mg BID dosing with a meal using fipaxalparant (HZN-825) Aptuit and Siegfried Barbera S.L. tablets are expected to achieve similar steady-state C_{trough} as observed in the Phase 2a trial in subjects with SSc and is selected as the higher dose in this trial. Additionally, there was less than dose-proportional increase in systemic exposures of fipaxalparant (HZN-825) from 150 mg to 300 mg (about 30% and 40% increase in C_{max} and AUC, respectively) and no exposure increase from 300 mg to 450 mg with Aptuit tablets; also, food intake increased fipaxalparant (HZN-825) exposures. Therefore, a second, less-frequent dose regimen, 300 mg QD with a meal, is selected to provide a broad range of fipaxalparant (HZN-825) exposures (2-fold different for AUC and ~6-fold different for steady-state C_{trough}) for evaluation in this trial, a dose that is still expected to achieve pharmacologically active steady-state C_{trough} above the concentrations needed for in vitro inhibition of $LPAR_1$ activity. Additionally, after adjusting for plasma protein binding of fipaxalparant (HZN-825) between humans and rats (99.97% and 99.92%, respectively), both 300 mg QD and 300 mg BID are also expected to achieve $AUC_{0\text{-}12h}$ above the $AUC_{0\text{-}12h}$ that showed efficacy in the rat DOCA model.

In summary, the plasma exposures associated with both fipaxalparant (HZN-825) 300 mg QD and 300 mg BID are anticipated to be well-tolerated and have clinical efficacy. The range of exposures achieved with these dose regimens will support efficient dose-range exploration and allow exposure-response evaluation of fipaxalparant (HZN-825) in subjects with IPF.

8 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, OLE.

8.1 Part 1 (Core Phase)

The overall objective of the Core Phase is to investigate the efficacy, safety, and tolerability of 2 dose regimens of fipaxalparant (HZN-825), a selective antagonist of $LPAR_1$, administered QD or BID for 52 weeks in the treatment of subjects with IPF.

8.1.1 Primary Objective

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

8.1.2 Secondary Objectives

1. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the proportion of subjects with decline in FVC % predicted ≥10% from Baseline after 52 weeks of treatment.
2. Evaluate the effect of 2 dose regimens of fipaxalparant (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 fipaxalparant (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 fipaxalparant (HZN-825) versus placebo on the living with IPF (L-IPF) after 52 weeks of treatment.
5. Evaluate the effect of 2 dose regimens fipaxalparant (HZN-825) versus placebo on the Leicester Cough Questionnaire (LCQ) after 52 weeks of treatment.
6. Evaluate the effect of 2 dose regimens of fipaxalparant (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 fipaxalparant (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 fipaxalparant (HZN-825), inclusive of, but not limited to, AEs, SAEs, and AESI.
9. Evaluate the PK of fipaxalparant (HZN-825).

8.1.3 Exploratory Objectives

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on mortality due to respiratory deterioration up to 52 weeks of treatment.
7. [redacted]
8. [redacted]

8.2 Part 2 (Extension Phase)

The overall objective of the Extension Phase is to investigate the long-term efficacy, safety, and tolerability of fipaxalparant (HZN-825), a selective antagonist of $LPAR_1$, 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 fipaxalparant (HZN-825) in Extension Phase

- Fipaxalparant (HZN-825) Baseline, defined as the latest measurement prior to the first dose of fipaxalparant (HZN-825) in either the Core Phase or the Extension Phase. For subjects who received placebo in the Core Phase, OLE Baseline will be the same as fipaxalparant (HZN-825) Baseline.

8.2.1 Primary Objective

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

8.2.2 Safety Objective

The safety objective is to examine the safety and tolerability of 52 weeks of open-label treatment with fipaxalparant (HZN-825) based on:

- TEAE assessment
- Concomitant medication use
- Vital signs
- 12-lead electrocardiogram (ECG)
- Clinical safety laboratory results

8.2.3 Exploratory Objectives

The exploratory efficacy objective is to evaluate the efficacy of 52 weeks of open-label treatment with fipaxalparant (HZN-825) via additional efficacy measurements:

- Proportion of subjects with decline in FVC % predicted ≥10%
- 6MWT
- K-BILD
- L-IPF
- LCQ
- [redacted]
- Hospitalization due to respiratory distress
- Composite endpoint of PFS, where progression includes decline in FVC % predicted ≥10% or death
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

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

9 INVESTIGATIONAL PLAN

9.1 Overall Trial Design and Plan

HZNP-HZN-825-303 (HARBOR) will be conducted at approximately 85 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 fipaxalparant (HZN-825) in subjects with IPF. Part 2 (Extension Phase) is an optional, open-label, repeat-dose, multicenter extension of the Core Phase.

Design of the Core Phase of the Trial

This is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter trial to evaluate the efficacy, safety, and tolerability of fipaxalparant (HZN-825) in subjects with IPF. Subjects will be screened within 8 weeks prior to the Baseline (Day 1) Visit. Approximately 135 subjects who meet the trial eligibility criteria will be randomly assigned in a 1:1:1 ratio on Day 1 to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (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 the 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.

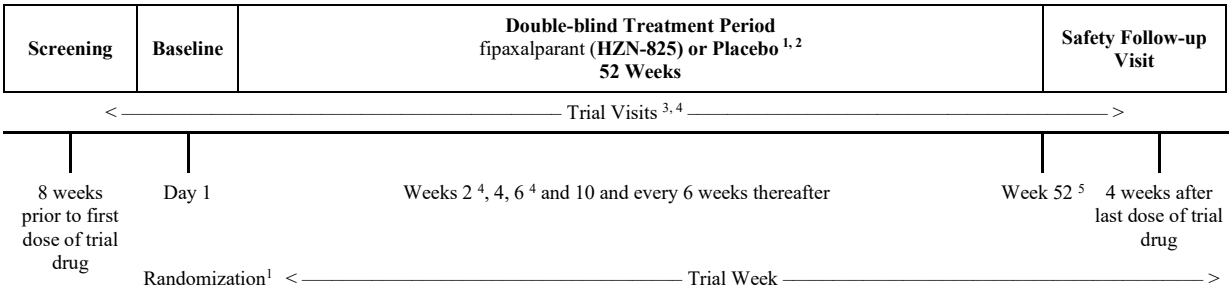
An interim analysis with a futility analysis will be performed [redacted] These unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC) and will be used to inform conduct of the current trial. The IDMC will include at least 1 statistician and at least 2 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 9.1 and details of trial activities during the Core Phase are provided in Section 2.1, *Schedule of Assessments During the Core Phase*.

Figure 9.1 Schematic of Trial Design – Core Phase



BID=twice daily; QD=once daily

1. Subjects will be randomized in a 1:1:1 ratio to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (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 the 52-week Extension Phase of the trial.

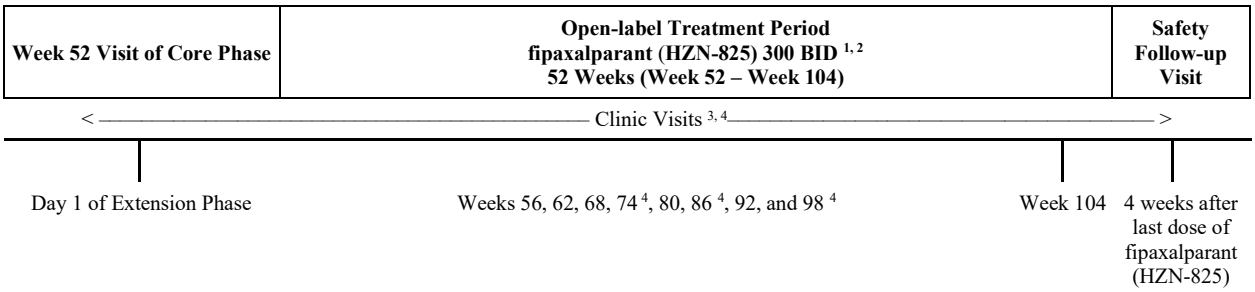
Design of the Extension Phase of the Trial

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 fipaxalparant (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 fipaxalparant (HZN-825).

If a subject prematurely discontinues fipaxalparant (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 fipaxalparant (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 Extension Phase trial design is presented in Figure 9.2 and details of trial activities during the Extension Phase are provided in Section 2.2, *Schedule of Assessments During the Extension Phase*.

Figure 9.2 Schematic of Trial Design – Extension Phase



BID=twice daily
1. The fipaxalparant (HZN-825) dose may be modified based on the results of the Core Phase.
2. If a subject prematurely discontinues open-label fipaxalparant (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 fipaxalparant (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.

9.1.1 Adjudication Committee

Cases of respiratory hospitalizations and acute exacerbations will each be reviewed by an independent adjudication committee in a blinded manner before database lock for the Core Phase of the trial. Details outlining the responsibilities of the adjudication committee and the parameters related to these events of interest will be included in the adjudication committee charter.

9.2 Discussion of Trial Design

This trial is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter trial in subjects with IPF that was designed according to standard principles. The measurements used in this trial to assess safety and efficacy are established and well-defined.

A treatment duration of 12 months was the length of exposure to trial drug in randomized, double-blind, placebo-controlled registrational clinical trials of IPF for pirfenidone [King et al., 2014] and nintedanib [Richeldi et al., 2014] and was sufficient to observe separation from placebo with respect to change in FVC % predicted. Receipt of placebo longer than 12 months would not be ethical in subjects with IPF, a progressive, debilitating and fatal disease. The Extension Phase of this clinical trial will allow subjects to receive up to 24 months of treatment with fipaxalparant (HZN-825), as well as limit the duration subjects are exposed to placebo. Subjects will be allowed to continue standard-of-care treatments, within guidelines outlined in the protocol, as well as protocol-permissible rescue therapy.

9.3 Selection of Trial Population

9.3.1 Eligibility Criteria for the Core Phase

9.3.1.1 Inclusion Criteria

Eligible subjects must meet/provide **all** of the following criteria:

1. Written informed consent.
2. Male or female ≥18 years of age at Screening.
3. Current diagnosis of IPF, as defined by ATS/ERS/JRS/ALAT guidelines [Raghu et al., 2022] and determined by central review; the date of initial diagnosis of IPF should be ≤7 years prior to Screening.
4. No recent changes or planned changes to the dose or regimen for IPF therapy, defined as:
   - Receiving a stable dose of IPF-approved therapy (i.e., nintedanib or pirfenidone) for a minimum of 3 months prior to Day 1 with no plans to change the background regimen during trial participation, or
   - Not currently receiving background IPF-approved therapy at Screening (either naïve to IPF-approved therapy or previously discontinued any IPF-approved therapy at least 4 weeks prior to Day 1 or drug-specific, 5 half-lives elimination period if longer than 4 weeks), and with no current plans to restart treatment during trial participation
   - Subjects receiving any additional agent for IPF therapy must be on a stable regimen for at least 3 months prior to Day 1 with no current plans to change the treatment regimen during trial participation. Any previously discontinued therapy used to treat IPF must have been discontinued at least 4 weeks prior to Day 1 or 5 half-lives for that specific therapy must have elapsed, whichever is longer, with no plans to restart the therapy during trial participation.
5. Lung HRCT historically performed within 6 months prior to the Screening Visit and according to the minimum requirements for IPF diagnosis by central review based on subject's HRCT. If an evaluable HRCT is not available within 6 months prior to Screening, an HRCT will be performed at Screening to determine eligibility, according to the same requirements as the historical HRCT. The HRCT must demonstrate a usual interstitial pneumonia or probable usual interstitial pneumonia pattern based on central review vendor interpretation. Histopathology in combination with HRCT results supportive of an IPF or IPF likely diagnosis according to Raghu et al., 2022 can be submitted to support subject eligibility.
6. HRCT shows ≥10% to <50% parenchymal fibrosis (reticulation) and the extent of fibrotic changes is greater than the extent of emphysema on the most recent HRCT scan (central reviewer determined).
7. Meets all of the following criteria during the Screening Period, as determined by central review:
   a. FVC ≥45% predicted of normal
   b. forced expiratory volume in 1 second /FVC ≥0.7
   c. DLCO corrected for hemoglobin is ≥25% and ≤90% predicted of normal
8. Estimated minimum life expectancy of ≥30 months for non-IPF-related disease, in the opinion of the Investigator.
9. Vaccinations are up to date, according to the Investigator’s discretion, given age, comorbidities, and local availability prior to trial drug dosing.
10. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

9.3.1.2 Exclusion Criteria

Subjects will be ineligible for trial participation if they meet **any** of the following criteria:

1. Any of the following cardiovascular diseases:
   a. uncontrolled, severe hypertension (≥160/100 mmHg), within 6 months of Screening
   b. myocardial infarction within 6 months of Screening
   c. unstable cardiac angina within 6 months of Screening
2. ILD associated with known primary diseases (e.g., sarcoidosis, amyloidosis, and coronavirus disease 2019 [COVID-19]), connective tissue disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjogren's, dermatomyositis, scleroderma), exposures (e.g., radiation, silica, asbestos, and coal dust) or drugs (e.g., amiodarone).
3. Known active bacterial, viral, fungal, mycobacterial, or other infection, including tuberculosis or atypical mycobacterial disease (fungal infections of nail beds are allowed). The subject must be 3 months beyond any acute infection with COVID-19 if there has been a prior infection.
4. Clinically significant pulmonary hypertension requiring chronic medical therapy.
5. Use of any of the following therapies within 4 weeks prior to Screening, during the Screening Period or planned during the trial: prednisone at steady dose >10 mg/day or equivalent or cyclosporine. Change in regimen or dosage of any immunosuppressant during the Screening Period through the end of trial participation will require consultation with and approval by the trial Medical Monitor. See Section 9.4.9 for full details. Avoiding the use of listed prohibited treatments must not be considered detrimental and must be indicated by the treating physician. Subjects must not be withdrawn from any standard-of-care treatment that is considered necessary for the clinical management of the subject in order to fulfill the trial eligibility requirements.
6. Use of rifampin within 2 weeks prior to Day 1 or planned during the trial.
7. Malignant condition in the past 5 years (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
8. Women of childbearing potential (WOCBP) or male subjects not agreeing to use highly effective method(s) of birth control throughout the trial and for 4 weeks after last dose of trial drug. Females must refrain from egg/ova donation for 4 weeks after the last dose of trial drug and males must refrain from sperm donation for 3 months after the last dose of trial drug. Women are considered of childbearing potential if they are not postmenopausal and not surgically sterile (documented bilateral salpingectomy, bilateral oophorectomy, or hysterectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Fertile male subjects must use a condom throughout the trial and for 4 weeks after the last

dose of trial drug. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

9. Pregnant or lactating women and women who plan to become pregnant or breast feed during the trial and within 4 weeks after the last dose of trial drug.
10. Current drug or alcohol abuse or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the subject.
11. Previous enrollment in this trial or participation in a prior fipaxalparant (HZN-825) or SAR100842 clinical trial.
12. Known history of positive test for human immunodeficiency virus (HIV). 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.
13. Active hepatitis (any of the following at Screening):

    Hepatitis B:
    - positive hepatitis B surface antigen
    - positive for anti-hepatitis B core antibody (anti-HBcAb) and a positive test for hepatitis B surface antibody (HBsAb) and presence of hepatitis B virus DNA
    - positive for HBcAb and a negative test for HBsAb and presence of hepatitis B virus DNA

    Hepatitis C:
    - positive anti-hepatitis C virus (anti-HCV) and positive HCV RNA.
14. Current alcoholic liver disease, primary biliary cirrhosis or primary sclerosing cholangitis.
15. Previous organ transplant (including allogeneic and autologous marrow transplant).
16. INR >2, prolonged prothrombin time >1.5 × the upper limit of normal (ULN) or partial thromboplastin time >1.5 × ULN at Screening.
17. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 × ULN.
18. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 at Screening.
19. Total bilirubin >1.5 × ULN. Subjects with documented diagnosis of Gilbert's syndrome may be enrolled if their total bilirubin is ≤3.0 mg/dL.
20. Moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment according to the Child-Pugh scoring system.
21. Any confirmed Grade 3 or higher laboratory abnormality.
22. Any laboratory abnormality at Screening that, in the opinion of the Investigator, would preclude the subject's participation in the trial.
23. Exposure to an experimental drug or experimental vaccine within either 30 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is the longest, prior to Day 1.
24. Any other condition that, in the opinion of the Investigator, would preclude enrollment in the trial.

9.3.2 Eligibility Criteria for the Extension Phase

9.3.2.1 Inclusion Criteria

Eligible subjects must meet/provide **all** of the following criteria:

1. Written informed consent.
2. Completed the Double-blind Treatment Period (Week 52) of the Core Phase of the trial; subjects prematurely discontinued from trial drug in the Core Phase of the trial for reasons other than safety or tolerability may be included at the discretion of the Investigator after completing scheduled visits, including Week 52 assessments.
3. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the Extension Phase of the trial.

9.3.2.2 Exclusion Criteria

Subjects will be ineligible for trial participation if they meet **any** of the following criteria:

1. Anticipated use of another investigational agent for any condition during the course of the trial.
2. New diagnosis of malignant condition after enrolling in Trial HZNP-HZN-825-303 (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
3. Estimated minimum life expectancy ≤18 months, in the opinion of the Investigator.
4. WOCBP or male subjects not agreeing to use highly effective method(s) of birth control throughout the trial and for 1 month after last dose of fipaxalparant (HZN-825). Male subjects must refrain from sperm donation and females from egg/ova donation for this same time period. Women are considered of childbearing potential if they are not postmenopausal and not surgically sterile (documented bilateral salpingectomy, bilateral oophorectomy, or hysterectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
5. Pregnant or lactating women.
6. Any other new development of the disease/condition/significant laboratory test abnormality during the course of the Core Phase of the trial, in the opinion of the Investigator, that would potentially put the subject at unacceptable risk.
7. In the opinion of the Investigator, unlikely to comply with the trial protocol or has a concomitant disease or condition that could interfere with the conduct of the trial.

9.3.3 Removal of Subjects from Treatment or the Trial

All subjects are free to withdraw from trial participation at any time, for any reason and without prejudice to their further medical care. In addition, the Investigator may terminate a subject from treatment at any time, if further treatment in the trial is not in the best interest of the subject.

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 discontinuation occurs during the Core Phase) or Week 104 (if discontinuation occurs during the Extension Phase). 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 (if discontinuation occurs during the Core Phase) or Week 104 (if discontinuation occurs during the Extension Phase) assessments. Subjects will be asked to return to the clinic for a Safety Follow-up Visit 4 weeks after the last dose of fipaxalparant (HZN-825).

9.3.3.1 Removal of Subjects from Treatment

9.3.3.1.1 Removal of Subjects from Trial Drug

The primary reason for discontinuation from trial drug should be recorded on the eCRF using one of the following categories:

- AE or clinically significant laboratory/ECG abnormality. The subject experiences an AE or clinically significant laboratory/ECG abnormality that imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue receiving treatment because of an AE or clinically significant laboratory/ECG abnormality. Subjects who discontinue trial drug due to an AE or clinically significant laboratory/ECG abnormality will remain in the trial unless they withdraw from the trial for another reason. In such cases, if situation is not an immediate emergency, the Investigator should contact the trial Medical Monitor.
- Drug-induced liver injury. Trial drug discontinuation should be considered if:
    - ALT or AST >8 × ULN
    - ALT or AST >5 × ULN for more than 2 weeks
    - ALT or AST >3 × ULN and (total bilirubin >2 × ULN or INR >1.5)
    - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

  Subjects who have ALT or AST levels >3 × ULN confirmed in a repeat test need to undergo close observation as prescribed by the FDA guidance on drug-induced liver injury. Close observation includes repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the subject is asymptomatic. The decision to rechallenge the subject is to be discussed and agreed upon by the Investigator, and Amgen Medical Monitor.
- Lack of efficacy. Discontinuation of trial drug due to lack of efficacy is at the discretion of the Investigator or subject and may occur if the Investigator determines that trial drug administration is not benefiting the subject. Subjects who discontinue trial drug due to lack of efficacy during the Core Phase will remain in the trial for scheduled safety and efficacy assessments through Week 52 unless they also withdraw from the trial for another reason. Subjects who discontinue trial drug due to lack of efficacy during the

Extension Phase will remain in the trial for scheduled safety and efficacy assessments through Week 104 unless they also withdraw from the trial for another reason.

- Restricted medications. Initiation of any therapy prohibited in the trial per Table 9.1 or use of any rescue medications prior to Week 28 may lead to subject discontinuation from treatment (see Section 9.4.9). The Investigator may consult with the trial Medical Monitor before initiation of the restricted medications.
- Withdrawal by subject. The subject wishes to withdraw from trial treatment. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF.
- Investigator's decision.
- Trial terminated by Sponsor. The Sponsor, external review bodies or regulatory agency terminates the trial.
- Pregnancy. The subject is removed from trial drug but not the trial; the subject continues with protocol-specified visits.
- Death.
- Completed. The subject completed treatment.
- Lost to follow-up. The subject does not participate in scheduled assessments and does not respond to the site's attempts to contact the subject. Before the subject is deemed 'lost to follow-up,' the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Subjects who prematurely discontinue trial drug during the Core Phase will be encouraged to continue trial participation in all planned visits, particularly returning for the Week 52/premature discontinuation assessments. Subjects who prematurely discontinue trial drug during the Extension Phase will be encouraged to continue trial participation in all planned visits, particularly returning for the Week 104/premature discontinuation assessments. Subjects who discontinue trial drug due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained, in addition to being encouraged to continue participation in all planned assessments.

9.3.3.1.2 Changes to Background Therapy for IPF

Subjects who change or discontinue standard of care therapy for IPF and/or another agent used to treat IPF should continue treatment with randomized investigational product for the planned duration of the trial unless removal of trial drug is also required due to meeting requirements listed in Section 9.3.3.1.1. The primary reason for change in background therapy should be recorded within the eCRF.

9.3.3.2 Removal of Subjects from the Trial

The primary reason for discontinuation from the trial should be recorded on the eCRF using one of the following categories:

- Lost to follow-up. The subject does not participate in scheduled assessments and does not respond to the site's attempts to contact the subject. Before the subject is deemed 'lost to follow-up,' the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Withdrawal by subject/guardian. The subject wishes to withdraw from the trial. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF.
- Death.
- Completed. The subject completed the Core Phase, including the Safety Follow-up Visit (if the subject does not enroll into the Extension Phase) or the subject completed the Extension Phase, including the Safety Follow-up Visit.
- Trial terminated by Sponsor.

9.3.4 Discontinuation of a Treatment Group or the Trial

The following events, if applicable, may cause premature termination of the clinical trial or trial arms: unjustifiable risk and/or toxicity in risk-benefit analysis (decision taken by Sponsor or representative), e.g., when AEs occur, unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile (substantial changes in risk-benefit considerations), and, therefore, medical and/or ethical reasons affect the continued performance of the trial; new scientific evidence becomes available during the trial that could affect the subject's safety (benefit-risk analysis no longer positive), e.g., new insights from other clinical trials; request of the Sponsor with or without recommendation from a data safety monitoring board, or of a regulatory agency, e.g., as a consequence of inspection; favorable opinion withdrawn by the ethics commission; in case of difficulties in the recruitment of the planned number of subjects in the indicated time (insufficient recruitment rate); and withdrawal of the license to manufacture (and/or of the permission to import).

9.3.5 Replacement Policy

9.3.5.1 Subjects

In general, no subject prematurely discontinued from the trial for any reason will be replaced. An exception may be made for subjects who are unevaluable due to the impact of an external event, for example, a pandemic or a natural disaster and associated restrictions on movement and work. Subjects unable to receive treatment or be evaluated due to restrictions during the event may be replaced, at the discretion of the Sponsor. This may result in more subjects being enrolled into the trial to allow for the planned number to be evaluable for the efficacy and safety analyses.

9.3.5.2 Centers

Prior to a site being recommended for closure, the site Principal Investigator, Medical Monitor, Trial Manager and possibly the Site Monitor will discuss the decision for closure.

A center may be closed and/or replaced for the following administrative reasons:

- Excessively slow recruitment.
- Unacceptable protocol adherence.

9.3.5.3 Screen Failures

Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria will be considered screen failures. An abnormal test during Screening may be repeated once during the Screening Period.

Screen failures may be allowed to rescreen for the trial if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that the subject can satisfy all of the eligibility criteria.

9.4 Treatments

9.4.1 Treatments Administered

During the Core Phase of the trial, on Day 1 of the Double-blind Treatment Period, subjects will be randomized in a 1:1:1 ratio to receive for 52 weeks:

1. Fipaxalparant (HZN-825) 300 mg QD, or
2. Fipaxalparant (HZN-825) 300 mg BID, or
3. Placebo.

During the Extension Phase, all subjects will receive open-label fipaxalparant (HZN-825) 300 mg BID for 52 weeks. The dose for the Extension Phase may be modified based on the results of the Core Phase.

9.4.2 Identity of Investigational Products

9.4.2.1 Fipaxalparant (HZN-825)

Fipaxalparant (HZN-825) is a selective antagonist of $LPAR_1$. Fipaxalparant (HZN-825) will be provided as film-coated tablets for oral administration. The oblong, white tablets contain fipaxalparant (HZN-825) 150 mg and the following excipients: [redacted]

9.4.2.2 Placebo

Placebo tablets match the appearance of active tablets and include the following excipients: [redacted]

9.4.3 Labeling

Fipaxalparant (HZN-825) 150 mg and placebo tablets will be packaged in blister packs (blister packs will be blinded for the Core Phase) according to the dose regimens identified in Section 9.4.1. Trial drug packaging will be in compliance with Sponsor/contract research organization standard procedures and will meet all local requirements. Each blister pack label will be labeled with a unique number.

Upon arrival of investigational products at the site, the Investigator (or designee in accordance with institutional policies and local regulations) should inspect them for damage and verify proper identity, quantity, integrity of seals and temperature conditions and report any deviations or product complaints to the monitor/Sponsor upon discovery.

9.4.4 Storage

Fipaxalparant (HZN-825) tablets should be stored at controlled room temperature, per US Pharmacopeia, between 20°C and 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F to 86°F).

9.4.5 Drug Accountability

The Principal Investigator at each site is responsible for the control of all trial drug and must maintain adequate records of the receipt and disposition of all trial drug shipped to the trial center. Records will include receipt dates, condition at time of receipt, quantities received, quantities dispensed, quantities returned or destroyed and the identification numbers of the subjects who received trial drug.

Investigational clinical supplies will be received by a designated person(s) at the trial site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated assistants have access.

At the end of the trial or if the subject prematurely discontinues the trial, the subjects should return any unused or partially used trial drugs to the site.

9.4.6 Trial Drug Administration and Timing of Dose for Each Subject

Subjects will take 2 tablets of fipaxalparant (HZN-825) 150 mg and/or placebo orally in the morning and evening with a meal in the Core Phase. Subject will take 2 tablets of fipaxalparant (HZN-825) 150 mg orally in the morning and evening with a meal in the Extension Phase. In the event a subject misses a dose, the dose should be taken along with the next planned dose (evening or morning) with a meal such that 4 tablets (up to 600 mg) in total will be taken. Due to a less than dose-proportional increase in fipaxalparant (HZN-825) systemic exposure, the 600 mg dose taken in the event of a prior missed dose will be considered part of the planned dosing for this trial.

9.4.6.1 Dose Modifications, Interruptions and Delays

All dosing instructions are applicable for fipaxalparant (HZN-825) and placebo administration. Any completely missed dose should be recorded on the *Dosing Interruptions* eCRF.

9.4.6.1.1 Orthostatic Hypotension

Orthostatic hypotension is considered the AESI for this trial. Trial drug should be temporarily discontinued in the case of trial drug-related, newly developed and clinically significant orthostatic hypotension associated with clinical symptoms requiring medical intervention. Trial drug may be restarted at the discretion of the Investigator after the clinical symptoms have resolved and following consultation with the Sponsor trial medical monitor. Subjects should have normal blood pressure (BP) and heart rate with absence of symptoms related to orthostatic hypotension for at least 5 days prior to restarting.

See Section 9.5.5.5 for details of orthostatic hypotension assessment.

9.4.6.1.2 Drug-induced Liver Injury

Elevated hepatic transaminases have been evaluated to be an important identified risk with fipaxalparant (HZN-825). The events are mostly non-serious and transient. Refer to Section 9.3.3.1 for criteria regarding trial drug discontinuation due to drug-induced liver injury.

9.4.7 Method of Assigning Subjects to Treatment Groups

For the Core Phase of the study, a randomization schedule will be generated by an unblinded statistician not otherwise associated with the trial prior to shipment of any trial drug to the clinical sites. On Day 1 of the Double-blind Treatment Period, once all Baseline procedures other than administration of trial drug have been completed, authorized site personnel will use the interactive response technology (IRT) system to randomize the subject. The Investigator or designee will then use the IRT system to obtain dosing information and dispense the appropriate trial drug.

All subjects in the Extension Phase will receive open-label fipaxalparant (HZN-825).

9.4.8 Blinding and Unblinding

The subject, Investigator and all other trial site personnel, including Sponsor or designee monitors, will be blinded to the trial drug being administered during the Core Phase.

The trial blind should be broken only if the safety of a subject is at risk and the treatment plan depends on which trial drug he or she received. Unless the subject is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor or Sponsor's designee before unblinding the subject's data. If a subject's data are unblinded without prior knowledge of the Sponsor, the Investigator must notify the Sponsor as soon as possible and no later than the next business day. All circumstances surrounding the event must be clearly documented. Please refer to the instructions in the eCRF guidelines for unblinding a subject.

The Sponsor or designee will unblind the identity of the trial drug for a drug-related SAE for submission to health authorities and external review bodies according to applicable regulatory requirements. However, the results will not be shared with other Sponsor representatives or staff at trial sites. Details of subjects who are unblinded during the trial will be included in the clinical study report.

Unblinding for independent pharmacological analysis of biological samples or SAE reporting will be performed according to procedures in place to ensure integrity of the data.

All investigative site staff directly involved in this trial will remain blinded from Screening through analysis of the follow-up data and all site close-out visits. The Sponsor and its designees will be unblinded after the database lock following completion of all subjects in the Double-blind Treatment Period.

An IDMC will review unblinded safety and efficacy data on a scheduled basis during the Core Phase of the trial. An interim analysis with a futility analysis will be performed [redacted] 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.

The Extension Phase is open-label, and all subjects will receive fipaxalparant (HZN-825).

9.4.9 Concomitant Therapy and Restricted Medications

All concomitant treatment, including herbs and supplements, must be documented in the eCRF.

Medication use restricted during the trial is presented in Table 9.1.

Table 9.1 Restricted Medications

Medication	Restricted Time Period
Prednisone at steady dose >10 mg/day or equivalent or cyclosporine [1]	4 weeks prior to Screening through trial completion Topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed during the trial. Short bursts for acute illnesses (asthma, allergic reaction) are permitted.
Other immunosuppressant agents	Change in treatment regimen or dosage with any other immunosuppressant during the Screening Period through the end of trial participation will require consultation and approval by the trial Medical Monitor.
An investigational agent for any condition	4 weeks or 5 half-lives, whichever is longer, prior to Screening through trial completion
Drug/alcohol abuse	History of abuse within the past 2 years or abuse during trial
Rifampin [2]	2 weeks prior to dosing through trial completion
OATP inhibitors: clarithromycin and gemfibrozil BCRP inhibitor [3]: eltrombopag	3 days prior to dosing through trial completion

BCRP=breast cancer resistance protein; CYP=cytochrome P450; OATP=organic anion transporter polypeptide
1. Cyclosporine is also an OATP and BCRP inhibitor.
2. Rifampin is a CYP enzyme inducer and an OATP inhibitor.
3. Known clinical OATP and BCRP inhibitors include, but are not limited to, the drugs included in this table.

The INR may need to be monitored more frequently for subjects taking warfarin. Fipaxalparant (HZN-825) is a weak inhibitor of cytochrome P450 (CYP)2C9, increasing S-warfarin AUC by 23% and R-warfarin AUC by 13% in healthy subjects, with minimal impact on INR (the mean increase in INR at 24 hours post warfarin administration from Baseline was 14.2% without fipaxalparant (HZN-825) and 16.8% with fipaxalparant (HZN-825) treatment).

Caution should be exercised when co-administering fipaxalparant (HZN-825) with other substrates of CYP2C9 or organic anion transporter (OAT)1/OAT3 that have narrow therapeutic windows.

Caution should be observed when co-administering fipaxalparant (HZN-825) with strong inhibitors of CYP2C9 or CYP2D6.

Fipaxalparant (HZN-825) and background therapy drugs (pirfenidone/nintedanib) are not expected to affect each other's exposure (see Section 7.1.3.4).

In case of a clinically significant deterioration in lung function, initiation of additional therapy or change in dose of background therapy or immunosuppressant therapy for IPF is allowed after Week 28 following consultation with the trial Medical Monitor. The addition or change of

background therapy for IPF treatment due to clinical deterioration will be labeled as "rescue therapy." Detailed (S)AE information following such events should be recorded in the eCRF.

Clinically significant deterioration includes:

- An absolute decline since Baseline in FVC % predicted ≥10% or an absolute decline since Baseline in FVC % predicted ≥5% to 9% with associated decline in DLCO ≥15% since Baseline, or

- Clinically significant deterioration in other organ systems, per Investigator assessment.

Other causes for FVC decline (i.e., respiratory tract infection) should be excluded. Repeat FVC/spirometry should be performed and confirmed prior to initiation of rescue medication if, to the Investigator's clinical judgment, well-founded doubts in the test's quality and the subject's good condition justify the associated delay in subject care, and the increase in risk for the subject.

9.4.10 Treatment Compliance

The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

Subjects who are not compliant with trial drug dosing should be counseled about the importance of taking trial drug on time and regularly.

An inventory of the trial drug supplies will be performed by the site or authorized trial designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent.

9.5 Efficacy and Safety Variables

Refer to the Schedules of Assessments (Section 2.1 and Section 2.2) for timing of all assessments.

9.5.1 Efficacy Variables

9.5.1.1 Spirometry

Spirometry, including FVC % predicted, will be assessed using a device provided by the Sponsor. Spirometry should only be performed by a trained assessor and the same assessor should complete the procedure for a given subject throughout the duration of the trial, unless it is not possible. For spirometry at Screening, the central review results are required for determination of eligibility.

Spirometry measurements must be performed according to ATS/ERS 2019 guidelines [Graham et al., 2019] whenever possible. The test will be done in triplicate (3 curves to be provided) and the best result selected according to the guidelines. The best of 3 efforts will be defined as the highest FVC, obtained on any of the 3 blows meeting the ATS/ERS criteria with a maximum of 8 maneuvers.

Spirometry measurements should be attempted at approximately the same time of day from Baseline onwards. On days of clinic visits, subjects must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Smoking should be discouraged throughout the visit days and will not be permitted in the 30-minute period prior to spirometry. Subjects should also avoid cold temperatures, environmental smoke, dust or areas with strong odors (e.g., perfumes). If treated with bronchodilators, washout of 24 hours for long-acting and 8 hours for short-acting bronchodilators should be observed before spirometry.

Spirometry results will be electronically transmitted. To ensure the quality of primary endpoint measurement, a central spirometry review will occur. Results will be over-read by a central reader, confirmed by the clinical site and data will be transferred into the clinical database.

In addition, the subject will be asked the following anchor (additional) questions at the time points indicated in Section 2.1 and Section 2.2.

Rate the severity of your breathing problems over the last week:

- 0: no breathing problems
- 1: mild breathing problems
- 2: moderate breathing problems
- 3: severe breathing problems
- 4: very severe breathing problems

How have your breathing problems changed since the start of the trial?

- +3: very much better
- +2: much better
- +1: a little better
- 0: no change
- -1: a little worse
- -2: much worse
- -3: very much worse

9.5.1.2 6-minute Walk Test

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 ATS guidelines for the 6MWT [Lancaster, 2018; ATS Guidelines, 2002].

9.5.1.3 Titrated Oxygen Requirement

Oxygen titration will be performed to determine the lowest oxygen flow rate required to maintain an oxygen saturation ($S_{p,O2}$) of ≥96% in the standing position (TOR). Titration will begin with the subject breathing room air. $S_{p,O2}$ will be monitored for 1 minute. If the $S_{p,O2}$ is ≥96%, the test

will conclude. If $S_{p,O2}$ is <96%, the oxygen flow rate will be increased each minute to achieve a target $S_{p,O2}$ of ≥96% using the following titration steps: 1, 2, 3, 4, 5, 6, 8, 12, and 15 $L \cdot min^{-1}$.

9.5.1.4 Diffusing Capacity of the Lungs for Carbon Monoxide

The site will use its own DLCO equipment and conduct all measurements with the same DLCO equipment in case that several devices are available at the site. Single-breath DLCO measurement will be performed according to the ATS guideline on DLCO measurements, when possible [Graham et al., 2017]. Refer to the DLCO procedural manual for details. Sites may request, but will not be required, to have subjects attend unscheduled visits for repeat DLCO measurements when the initial measurement has not passed according to DLCO central review quality control criteria. DLCO assessments for determining subject eligibility for the trial can be repeated once during the 35-day Screening window. During the treatment period, repeat measurements should be attempted within 1 week, if possible. DLCO results that do not pass quality control and for which it is not practical to recall the subject to the trial site for a repeat test, Investigators should assess and record within the subject's source documents whether the DLCO performed was valid per the site's standard practices and correlates well with the subject's clinical conditions and previous DLCO results.

DLCO values will be adjusted for altitude when necessary, and the most recent hemoglobin value. An adjustment for carboxyhemoglobin will be made if the Investigator determines that the subject may have elevated carboxyhemoglobin. The DLCO assessment should always be performed after the FVC measurement and should always be started approximately the same time each day.

9.5.1.5 Lung High-resolution Computed Tomography

Lung HRCT will be reviewed by a central reader. These results must be available prior to randomization.

If HRCT has been performed for clinical care in the 6 months prior to Screening and has been reviewed and deemed acceptable per central reader, then HRCT need not be performed at Screening.

9.5.1.6 Patient-reported Outcome Assessments

Health outcomes assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments.

A copy of each assessment is provided in the Appendix (Section 17).

9.5.1.6.1 Living with IPF

The L-IPF is a validated questionnaire that assesses symptoms, disease impacts and health-related quality of life in subjects with IPF [Swigris et al., 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.

9.5.1.6.2 King's Brief Interstitial Lung Disease Questionnaire

The K-BILD is a self-completed health status questionnaire comprising 15 items and a 7-point Likert response scale that was developed and validated specifically for patients with IPF [Patel et al., 2012]. 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].

9.5.1.6.3 Leicester Cough Questionnaire

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 et al., 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.

9.5.1.6.4 SF-12 Health Survey

The SF-12 [Ware et al., 1996] is a 12-item survey used to assess general health-related quality of life. The SF-12 items are scored to generate a physical component score and mental component score (from the subject's perspective. The SF-12 examines 8 domains of health outcomes, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The SF-12 is a shorter version of the SF-36, which has accepted validity for use in subjects with IPF [Swigris et al., 2010; Tomioka et al., 2007] and is 1 of 4 questionnaires used in the IPF Prospective Outcomes, an ongoing observational US registry of patients with confirmed IPF that records patient-reported outcomes.

9.5.2 Pharmacokinetic Measurements

Blood samples will be collected from all subjects to evaluate the PK of fipaxalparant (HZN-825) at the time points shown in Table 9.2. For visits with post-dose PK samples, the morning dose regimen will be taken in the clinic. Note that all pre-dose samples will be collected prior to any trial drug administration during the clinic visit. For subjects not entering the 52-week Extension Phase, a sample will be collected anytime during the Week 52 Visit. PK sample collection time

and the most recent dosing time prior to PK sample collection will be recorded for all PK samples.

If the clinic visit is in the morning, on days when a pre-dose PK sample will be collected, subjects will be instructed to withhold taking trial drug before the visit, and drug and a meal will be administered in the clinic after the pre-dose PK samples are taken. Time of drug administration in the clinic as well as the most recent dosing time prior to the visit will be recorded; 1 additional PK sample will be collected 2 to 4 hours after dosing in the clinic during the Week 16, Week 28, and Week 56 Visits.

If the clinic visit is in the afternoon, on days when a pre-dose PK sample will be collected, subjects will be instructed to take trial drug before 8 a.m. with a meal and record dosing time; 1 PK sample will be collected anytime during the clinic. For the Week 16, Week 28, and Week 56 Visits, subjects will receive the evening dose during the visit (dosing time to be recorded) if it is at least 8 hours from the morning dosing. An additional PK sample will be collected 2 to 4 hours post-dose; otherwise, subjects will be instructed to take the evening dose at regular dosing time and no post-dose PK sample will be collected.

Instructions for collection, processing, handling, storing and shipping of PK samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.

Table 9.2 Schedule of Pharmacokinetic Sample Collection

Time point	Pre-dose	2 to 4 Hours Post-dose	Anytime During Visit
Core Phase			
Day 1		X	
Week 4	X		
Week 10			X
Weeks 16 and 28	X	X	
Weeks 40 and 52	X		
Extension Phase			
Day 1 (Week 52 of Core Phase)	X		
Week 56	X	X	
Week 68	X		
Week 80	X		
Week 92	X		

9.5.3 Pharmacogenetic Assessments

An optional blood sample will be collected from all subjects providing consent and may be analyzed to explore the impact of polymorphisms in genes encoding drug metabolizing enzymes and/or transporters (e.g., cytochrome P450 CYP2C9, CYP2D6, solute carrier organic anion

transporter family member [SLCO] 1B1 and SLCO1B3) on fipaxalparant (HZN-825) PK. These samples will be stored no longer than 5 years.

Instructions for collection, processing, handling, storing and shipping of samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.

9.5.4 Pharmacodynamic Assessments

Blood samples will be taken during the trial to evaluate the pharmacodynamic effect of fipaxalparant (HZN-825). Serum samples will be taken at the following visits: Day 1 (pre-dose), Week 16 (pre-dose), Week 28 (pre-dose), Week 52 (pre-dose), Week 80 (pre-dose) and Week 104 (pre-dose). Samples will be stored frozen for potential analysis of biomarkers of the $LPAR_1$ pathway or IPF disease. All samples will be destroyed after potential biomarkers have been tested or 5 years after the trial is complete, whichever comes first.

A blood sample will be taken at Day 1 (pre-dose), Week 28 (pre-dose), Week 52 (pre-dose), Week 80 (pre-dose) and Week 104 (pre-dose) for gene expression profiling of peripheral blood mononuclear cells as it relates to disease biology. Instructions for collection, processing, handling, storing and shipping of samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.

9.5.5 Safety Variables

Safety will be assessed via AEs, concomitant medication use, physical examinations, vital signs, orthostatic hypotension assessment, laboratory evaluations, 12-lead ECG, and echocardiogram.

9.5.5.1 Adverse Events

9.5.5.1.1 Definitions

9.5.5.1.1.1 Adverse Event Definition

According to ICH, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

Exacerbation of a chronic or intermittent pre-existing condition that worsens in intensity or increases in frequency during a trial is to be reported as an AE.

Unchanged, chronic conditions are **NOT** considered AEs and should not be recorded on the AE pages of the eCRF unless there is a clear exacerbation of a chronic condition.

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the trial drug is being studied (i.e., IPF). It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events that are unequivocally due to disease progression should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of trial drug.

9.5.5.1.1.2 Serious Adverse Event Definition

A TEAE, baseline event or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following:

- Death. This includes any death that occurs during the conduct of a clinical trial, including deaths that appear to be completely unrelated to the trial drug (e.g., car accidents).
- Life-threatening adverse experience. An AE or suspected adverse reaction is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Persistent or significant disability or incapacity.
- Inpatient hospitalization or prolongation of an existing hospitalization.
- Congenital anomaly or birth defect.
- Other medically important event that, according to appropriate medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above.

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Elective surgeries that require hospitalization and treatment received at an emergency room or similar facility will not be considered as SAEs unless one of the definitions of an SAE listed above is met.

In addition, hospitalizations for planned procedures are not considered an AE, unless they are prolonged hospitalizations and emergency room visits <24 hours in duration are not considered hospitalizations.

9.5.5.1.1.3 Non-serious Adverse Event Definition

A non-serious AE includes any AE that is not described in the previous SAE category.

9.5.5.1.1.4 Adverse Events of Special Interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in

order to characterize and understand them. AESIs may be added or removed during a trial by protocol amendment.

The following AESI is identified for this trial:

- Orthostatic hypotension: The Sponsor will consider an event of orthostatic hypotension if the following definition is met: a reduction of systolic BP by ≥20 mmHg or reduction of diastolic BP by ≥10 mmHg **and** associated with symptoms such as lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, presyncope or syncope.
  The symptoms i.e., lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, presyncope, or syncope are reported by the patient throughout the orthostatic hypotension assessment, without the BP reductions (reduction of systolic BP ≥ 20 mmHg or diastolic BP ≥10 mmHg), then these symptoms will be recorded as AE.

Please note that the above-mentioned reported symptoms during orthostatic hypotension assessment should only be reported as adverse events separately if they meet any of the below criteria:

- The symptoms are severe and/or require medical interventions
- The symptoms were triggered by the orthostatic hypotension assessment maneuver and persisted for a significantly longer duration beyond the orthostatic hypotension assessment period
- The symptoms are assessed not due to the maneuver of orthostatic hypotension assessment

If these symptoms are reported in combination with the BP reductions, i.e., reduction of systolic BP ≥20 mmHg or diastolic BP ≥10 mmHg, these symptoms will be considered part of the orthostatic hypotension event and will not be reported separately.

Orthostatic hypotension assessment procedure will be performed during the Core Phase (as outlined in Section 2.1 on Day 1 and at Weeks 4, 28, and 52/premature discontinuation) and the Extension Phase (as outlined in Section 2.2 on Day 1 [Week 52 of Core Phase] and at Weeks 56, 80 and 104/premature discontinuation), as is detailed in the Orthostatic Hypotension Assessment Manual in Section 17.9.

If symptoms are reported by the subject throughout the assessment, without the BP reductions noted above, then the symptoms will be recorded separately as AEs and orthostatic hypotension will not be recorded.

Signs and symptoms associated with orthostatic hypotension reported outside of the assessment will be captured as part of spontaneously reported AEs at each visit.

Depending on the timing, nature and severity of these spontaneous AEs, additional investigations will be conducted at the next scheduled visit or at an unscheduled visit, as clinically indicated per the Investigator's judgment. Whenever possible, the following data should be collected: concomitant medications, and BP and heart rate measurements in supine and standing positions. Depending on the severity, plasma glucose level and ECG should be obtained per Investigator's clinical judgment.

9.5.5.1.2 Documentation of Adverse Events

Any AEs that occur after signing the ICF and prior to dosing on Day 1 will be considered medical history. The TEAE reporting period begins with administration of the first dose of trial drug on Day 1 and continues until 4 weeks after the last dose of trial drug or premature discontinuation. All medical history, TEAEs and AEs must be recorded in the source documents and on the subject's eCRF. All AEs and SAEs with onset after signing of informed consent through 4 weeks after the last dose of trial drug will be recorded. If a subject discontinues due to an SAE, that subject will be followed as per Section 9.5.5.1.5.

If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by trial drug, the Investigator will report this SAE using the procedures described in Section 9.5.5.1.5. The Investigator is responsible for collecting and documenting the outcome of AEs/SAEs.

If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, except for the subject number, will be blinded on the copies of the medical records before submission to the Sponsor.

Detailed information regarding all SAEs must also be recorded on the SAE Reporting Form. Whenever clinically appropriate, the Investigator should group together into a single term the signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis and sneezing might be grouped together as "upper respiratory infection" if the Investigator is confident of the diagnosis.

9.5.5.1.3 Intensity or Severity of Adverse Events

All AEs, both serious and non-serious, will be assessed for severity using the Rheumatology Common Toxicity Criteria v2.0 [Woodworth et al., 2007]. The scale displays Grades 1 through 4 with unique clinical descriptions of severity for each AE (including abnormal laboratory values) based on this general guideline.

- Grade 1 (mild) – asymptomatic or transient, short duration (<1 week), no change in lifestyle, no medication or over-the-counter drugs

- Grade 2 (moderate) – symptomatic, duration 1 to 2 weeks, alter lifestyle occasionally, medications give relief (may be prescription), trial drug continued

- Grade 3 (severe) – prolonged symptoms, reversible, major functional impairment, prescription medications/partial relief, hospitalized <24 hours, temporary trial drug discontinuation or/and dose reduced

- Grade 4 (includes life-threatening) – at risk of death, substantial disability, especially if permanent, hospitalized >24 hours, permanent trial drug discontinuation

9.5.5.1.4 Relationship or Causality to Trial Drug

The investigator is obligated to assess the relationship between investigational product(s) and each occurrence of each AE and SAE.

Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in their assessment.

For each AE/SAE, the investigator must document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which a SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data.

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The relationship of the trial drug to each AE will be determined by the Investigator and the Sponsor based on the following definitions:

- Not related: There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event.

- Related: There is evidence in favor of a causal relationship (i.e., there is a plausible time course) and at least one of the following criteria apply:

    - There is a reasonable pharmacological relationship (or known class effect).

    - There is no other more plausible explanation.

- There is a positive de-challenge (without active treatment of the event).
- There is a positive re-challenge.
- There is a distinguishable dose effect.

9.5.5.1.5 Reporting and Documenting Serious Adverse Events

All SAEs beginning with the time of signing of the ICF and continuing through 4 weeks after the last dose of trial drug must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to trial drug:

1. Report the SAE to the Sponsor by entering the information into the eCRF **immediately and not later than 24 hours** after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE Reporting form **immediately and not later than 24 hours** after becoming aware that a subject has experienced an SAE (see Section 17.1 for contact information).

   After the study is completed at a given site, the electronic data capture (EDC) system will be taken off-line to prevent the entry of new data or changes to existing data.

   If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the EDC system has been taken off-line, then the site can report this information on the paper-based SAE Reporting Form.

2. Perform appropriate diagnostic tests and therapeutic measures and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries and autopsy report to the Sponsor's representative.

3. Conduct appropriate consultation and follow-up evaluation until the SAE outcome is known or the SAE is resolved. Outcomes for reported AEs/SAEs/AESIs are to be defined as follows:

   - Recovering/Resolving
   - Recovered/Resolved
   - Not Recovered/Not Resolved
   - Recovered/Resolved with sequelae
   - Fatal
   - Unknown

4. All new information for previously reported SAEs must be sent to the Sponsor **immediately and no later than 24 hours** after Investigator's awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts

from the medical records. Information provided about the SAE must be consistent with that recorded on the Adverse Events eCRF.

There is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of SAEs suspected to be related to investigational product, then these SAEs will be reported to the Sponsor **immediately and no later than 24 hours** after the investigator's awareness of the event. SAEs reported after the end of the study will be captured within the safety database as clinical study cases and handled accordingly based on relationship to investigational product.

If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

Review each SAE report and evaluate the relationship of the SAE to trial treatment.

9.5.5.1.5.1 Monitoring of Serious Adverse Events Anticipated in the Trial Population

SAEs are anticipated to occur in the trial population independent of the subject's exposure to trial drug. These anticipated SAEs are provided in Section 17.8 (Serious Adverse Events Anticipated in the Trial Population) for reference. The list does NOT change the Investigator's reporting obligations or prevent the need to report an AE meeting the definition of an SAE, as detailed above. The purpose of this list is to alert the Investigator that some events reported as SAEs that are anticipated to occur in the trial population due to underlying disease, may not require expedited reporting to the regulatory authorities in every country/region. The Sponsor will monitor these events throughout the course of the trial for any change in frequency.

9.5.5.1.6 Follow-up of Adverse Events

The Investigator is obligated to follow up any reported AE, SAE, or AESI until all relevant clinical data are known to allow for an outcome or the event is resolved, in addition to confirming the causality assessment. Any ongoing trial drug-related AE present at the time of trial termination, including a clinically significant laboratory test abnormality, will be followed until the event is resolved or until the event stabilizes and the overall clinical outcome has been ascertained.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

If a subject is permanently withdrawn from investigational product(s) and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a SAE, this information must be submitted to Sponsor.

The investigator will submit any updated SAE data to Sponsor **immediately and no later than 24 hours** of receipt of the information.

9.5.5.1.7 Medication Errors

A medication error is any unintended failure in the drug treatment process, such as a mistake in the prescribing, dispensing, storing, preparation or administration of a medicine that leads to, or has the potential to lead to harm to the subject.

An overdose is defined as a known deliberate or accidental administration of investigational drug to a subject. For this trial, any dose of fipaxalparant (HZN-825) that is more than the dose that has been assigned will be considered an overdose.

An AE or SAE that is associated with a medication error, such as an overdose, is to be reported according to the procedures outlined in Sections 9.5.5.1.2 and 9.5.5.1.5, respectively. All medication errors or overdoses, with or without an AE or SAE, should be recorded as a protocol deviation and reported to the trial Medical Monitor in a timely manner. AEs or SAEs may not occur immediately after the medication error or overdose.

There is no clinical experience with overdose with fipaxalparant (HZN-825). No specific antidote or detoxification measures can be recommended to date. If accidental overdose is suspected, the subject should be treated symptomatically.

9.5.5.1.8 Review of Adverse Events and Emerging New Safety Information

The Sponsor will perform an ongoing review of all AEs and all other emerging new information relevant to the safety of the drug, including periodic review and analyses of cumulative safety data for the trial.

9.5.5.1.9 Reporting of Investigational New Drug Safety Reports

The Sponsor will report SAEs associated with fipaxalparant (HZN-825) to the appropriate regulatory authorities and all Investigators in accordance with the local and regional regulatory authorities laws and regulations.

9.5.5.1.10 Development Safety Update Reports

The Sponsor will prepare and submit annual safety reports to the FDA. Drug safety update reports will also be submitted to countries and territories as required.

The Sponsor will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report in the European Union [EU]) for the Sponsor investigational product. To ensure that consolidated safety information for the study is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical study, if applicable.

9.5.5.1.11 Regulatory Reporting Requirements for Safety Information

If subject is permanently withdrawn from investigational product(s), and/or noninvestigational product(s)/auxiliary medicinal product(s) because of a SAE, this information must be submitted to the Sponsor.

Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the external review body and investigators.

Individual safety reports for suspected unexpected serious adverse reactions will be reported by the Sponsor according to local regulatory requirements (e.g., electronic submission to the Eudravigilance database in the EU as per EU Clinical Trial Regulation 536/2014) as well as Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the external review body, if appropriate according to local requirements.

For studies in which the treatment assignment is blinded, to comply with worldwide reporting regulations for SAEs, the treatment assignment of subjects who develop serious, unexpected, and related AEs may be unblinded by the Sponsor before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related SAEs reports sent to regulatory authorities in accordance with local requirements.

9.5.5.1.12 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.

9.5.5.2 Pregnancy and Lactation Reporting

Pregnancy testing will be performed for WOCBP. Serum pregnancy tests will be analyzed at a central trial laboratory and the urine pregnancy tests will be performed locally. In addition, at-home pregnancy tests will be completed by WOCBP at Weeks 8, 12, 20, 24, 32, 36, 44, and 48 during the Core Phase and at Weeks 60, 64, 72, 76, 84, 88, 96 and 100 during the Extension Phase, and results will be reported to the site.

If a female subject becomes pregnant during the Double-blind Treatment Period, she should immediately notify the Investigator and trial drug dosing should be permanently discontinued but the subject will be asked to continue in the trial for evaluations.

Pregnancy occurring in the partner of a male subject participating in the trial should be reported to the Investigator and the Sponsor immediately upon awareness of pregnancy. Monitoring of the subject's partner should continue until conclusion of the pregnancy.

Subjects should be instructed to continue contraception for 4 weeks after their last dose of trial drug. Pregnancies occurring up to 4 weeks after the last dose of trial drug must also be reported to the Investigator.

Some examples of highly effective contraceptive methods that have a failure rate of <1% per year when used consistently and correctly are:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable
    - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation
- Vasectomized partner
- Sexual abstinence from heterosexual intercourse

There are no expected drug interactions between fipaxalparant (HZN-825) and hormonal contraceptives.

Abstinence should only be used as a contraceptive method if it is in line with the subject's usual and preferred lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods) is not an acceptable method of contraception.

Details of all pregnancies and/or lactation in female subjects and pregnancies in female partners of male subjects will be collected after the start of study treatment and until 4 weeks after last dose of trial drug.

If a pregnancy is reported, the investigator is to inform the Sponsor **immediately and no later than 24 hours** of learning of the pregnancy and/or lactation. The Investigator should report pregnancies to the Sponsor by submitting the completed Pregnancy Report Form **immediately**

and not later than 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see Section 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy. If pregnancy continues and the subject signs the pregnancy consent form, monitoring should also continue to the conclusion of the pregnancy and the outcome of the pregnancy should be reported to the Sponsor.

Lactation information will be recorded on the Lactation Notification Form and submitted to Sponsor Global Patient Safety **immediately and no later than 24 hours** of the investigator's awareness of the event.

9.5.5.3 Medical History

Medical history, including IPF history and treatment and substance use history, will be recorded.

9.5.5.4 Vital Signs, Weight and Height

BP and pulse measurements will be obtained with the subject's arm unconstrained by clothing or other material and while the subject is sitting up. When possible, the same arm will be used for measurements for all trial visits.

Weight and height measurements will be obtained. To limit the potential for variability in weight collection, the subject should wear lightweight clothing and no shoes during weighing.

9.5.5.5 Orthostatic Hypotension Assessment

Due to a potential role of LPA in vascular tone (Section 7.1.2), orthostatic hypotension will be assessed at the time points indicated in Section 2.1 and Section 2.2.

BP and heart rate will be measured after the subject has rested ≥5 minutes in the supine position and after 1 minute and 3 minutes in the standing position, as per the Orthostatic Hypotension Assessment Manual provided by the Sponsor. See Section 9.5.5.1.1.4 for more information on orthostatic hypotension assessment.

A copy of the Orthostatic Hypotension Assessment Manual is provided in Section 17.9.

9.5.5.6 Physical Examination

A complete physical examination, including but not limited to, cardiac, pulmonary and neurologic assessments, will be performed per the Schedules of Assessments (Section 2.1 and Section 2.2).

9.5.5.7 Electrocardiogram

ECG results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated by the Investigator as clinically significant or not clinically significant. Any clinically significant abnormal ECG, including a QT interval corrected for heart rate >450 ms, should be confirmed by a repeat resting ECG at the same visit. The site personnel should ensure that ECGs are collected after the subject is supine for at least 10 minutes.

A copy of the ECG tracing will remain with the source documents

9.5.5.8 Echocardiogram

A standard transthoracic echocardiogram will be conducted according to the Schedules of Assessments (Section 2.1 and Section 2.2). Echocardiogram results will be recorded on the eCRF as normal or abnormal and all abnormal results will be evaluated by the Investigator as clinically significant or not clinically significant. A copy of the echocardiogram results will remain with the source documents.

9.5.5.9 Laboratory Tests for Evaluation

A central trial laboratory will be used for all protocol-specified laboratory evaluations, with the exception of urine pregnancy tests that will be performed locally at each site or at-home, as applicable, in order to maintain monthly pregnancy testing.

Chemistry parameters to be evaluated include total protein, albumin, sodium, phosphate, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase, uric acid, glucose, lactate dehydrogenase; liver function tests (ALT, AST, gamma glutamyltransferase, alkaline phosphatase, total bile acid, total bilirubin, conjugated, and unconjugated bilirubin, if applicable).

Fasting glucose and fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides) will also be evaluated (see Sections 2.1 and 2.2).

Hematology parameters to be evaluated include hemoglobin, hematocrit, red blood cell count (with morphology if blood cell count is abnormal), mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, reticulocyte count, white blood cell count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes) and platelet count.

Urinalysis parameters to be evaluated include macroscopic panel (i.e., appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrites, pH, protein, specific gravity and urobilinogen) and microscopic panel (i.e., amorphous crystals, bacteria, calcium carbonate crystals, calcium oxalate crystals, calcium phosphate crystals, cysteine crystals, granular casts, hyaline casts, leucine crystals, mucus, red blood cells, renal epithelial cells, squamous epithelial cells, transitional epithelial cells, triple phosphate crystals, tyrosine crystals, uric acid crystals, waxy casts, white blood cells, white blood cell casts and yeast).

Samples for clinical inflammatory laboratory evaluation of high-sensitivity C-reactive protein will also be collected.

The total blood volume for planned visits through the final safety follow-up visit in the Core Phase is approximately 305 mL. Extension Phase, repeat or unscheduled blood tests performed in individual subjects may add to the total blood volume. Instructions for the collection, handling and analysis of clinical laboratory samples will be provided to the site prior to trial site initiation.

9.5.6 Appropriateness of Measurements

All safety and efficacy variables, as well as the methods to measure them, are standard variables/methods in clinical trials and/or clinical practice and are widely used and generally recognized as reliable, accurate and relevant.

The L-IPF [Swigris et al., 2020], K-BILD [Patel et al., 2012], LCQ [Birring et al., 2003] and SF-12 [Swigris et al., 2010; Tomioka et al., 2007] have been validated for use in subjects with IPF.

9.5.7 Trial Procedures

Trial procedures and timing are detailed in the Schedules of Assessments (Section 2.1 and Section 2.2).

Visits at Weeks 22, 34 and 46 during the Core Phase and at Weeks 74, 86, and 98 during the Extension Phase may be completed at an alternative remote location, e.g., a subject's home, by a visiting home healthcare professional and will be based on local availability and as allowable based on local laws and regulations. Remote locations will be discussed during the consent process per subject's preference and as approved by the Investigator. Site Investigators will have direct awareness and oversight of remote subject visits.

The end of the trial is defined as the date of the last visit of the last subject undergoing the trial.

9.5.8 Effect of a Pandemic on Trial Procedures

In rare situations due directly to COVID-19 where trial subjects cannot attend scheduled clinic visits, the following modifications may be considered:

- For efficacy assessments, a home visit or a subject-collected FVC may be used. For patient-reported outcomes or other questionnaires, a telephone visit, virtual visit or home visit may be used to collect information.
- For safety assessments, a local laboratory or a home visit may be used to collect laboratory-related assessments to monitor safety and results will be communicated to the Medical Monitor. A telephone visit, virtual visit or home visit may be used to collect information on AEs and drug compliance. Investigators may also consider shipping trial drug to a subject's home via appropriate courier, if necessary.
- If data are captured in an irregular manner (e.g., patient-reported outcomes via telephone or FVC in-home) this should be captured via source documentation. If possible, these protocol modifications should be discussed with the Sponsor and contract research organization prior to implementation, but deviations to immediately address subject safety are possible per the Investigator's discretion.

9.6 Statistical Methods and Determination of Sample Size

9.6.1 Core Phase

9.6.1.1 Endpoints

9.6.1.1.1 Primary Efficacy Endpoint

The primary endpoint is the change in FVC % predicted from Baseline to Week 52.

9.6.1.1.2 Key Secondary Efficacy Endpoint

Proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52.

9.6.1.1.3 Other Secondary Efficacy Endpoints

1. Change from Baseline in the 6MWT results to Week 52.
2. Change from Baseline in K-BILD scores to Week 52.
3. Change from Baseline in L-IPF scores to Week 52.
4. Change from Baseline in LCQ scores to Week 52.
5. Time to first hospitalization due to respiratory distress from Baseline up to Week 52.
6. Time to first onset of the composite endpoint of PFS from Baseline up to Week 52, where progression includes decline in FVC % predicted ≥10% or death.

9.6.1.1.4 Exploratory Endpoints

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. Time to death due to respiratory deterioration from Baseline up to Week 52.
7. [redacted]
8. [redacted]

9.6.1.1.5 Safety and Tolerability Endpoints

1. Incidence of TEAEs, SAEs and the AESI (orthostatic hypotension).
2. Concomitant medication use.
3. Vital signs.
4. 12-lead ECGs and echocardiograms.
5. Laboratory evaluations.

9.6.1.1.6 Pharmacokinetic Endpoint

1. Pre- and post-dose concentrations of fipaxalparant (HZN-825).

9.6.1.2 Analysis Sets

Three analysis sets will be defined for the Core Phase of the trial. The full analysis set (FAS) will include all subjects who are randomized to treatment and take at least 1 dose of trial drug. This will be the analysis set used for efficacy data analyses and subjects will be analyzed according to the treatment to which they were randomized. The safety analysis set will include all subjects who receive at least 1 dose or partial dose of trial drug. The PK analysis set will include all subjects who receive at least 1 dose or partial dose of fipaxalparant (HZN-825) and have at least 1 PK sample post fipaxalparant (HZN-825) treatment.

9.6.1.3 Primary Efficacy Endpoint Analysis

The estimand for the primary efficacy analyses will be constructed to compare the primary endpoint between each dose regimen of fipaxalparant (HZN-825) and placebo using the treatment policy strategy approach to intercurrent events. All subjects who are randomized and take at least 1 dose of trial drug will be included in the primary efficacy analyses (FAS).

The primary efficacy endpoint will be change from Baseline in FVC % predicted to Week 52. A mixed model for repeated measures (MMRM) analysis of covariance model will be fit to the data using observed change in FVC % predicted values from all planned post-Baseline assessments (i.e., Weeks 4, 16, 28, 40, and 52) with covariates of stratification factors (concomitant use of IPF therapy [yes, no] and FVC % predicted at Baseline [≥70%, <70%]), treatment group, visit and visit-by-treatment group interaction. The unstructured variance-covariance matrix will be used in the model. Treatment group least squares means, associated standard error (SE) and their differences (each fipaxalparant [HZN-825] group minus placebo separately), SE of the difference, 90% CIs and p-value overall and for each visit will be provided.

For subjects with missing data at 1 or more time points, the available data will be included in the analysis.

As a supplemental analysis to assess the robustness of the efficacy analysis results, the effect of each dose regimen of fipaxalparant (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 for the primary efficacy endpoint
- Cumulative response curve comparison using the Kolmogorov-Smirnov test on:
    - The range of improvement (≥0% to ≥15% with a 5% increment) and worsening (< -15% to <0% with a 5% increment) based on the change in FVC % predicted value from Baseline at Week 52
    - The range cut-off values from less than -300 mL to greater 100 mL with a 100-mL increment based on the change in FVC (in mL) from Baseline at Week 52

One sensitivity analysis will consider whether data missing not at random may change the conclusion. A tipping point analysis will estimate the difference in true values among unobserved data that must occur to change the conclusion for each dose (i.e., change the result for each dose from $p \leq 0.10$ to $p > 0.10$).

Potential intercurrent events such as discontinuing from the treatment, early discontinuing from the trial, initiating rescue therapy, death, lung transplant or potentially COVID-19, may occur during the trial. Intercurrent events will be addressed in the primary analysis by using treatment policy strategy with all available data. Supplemental analyses will assess the use of rescue medication. The proportion of subjects who qualify for and who receive rescue medication at each potential time point will be summarized for each treatment group to determine whether there are different use rates between treatment groups. A supplemental analysis will repeat the primary analysis except that it will ignore all FVC data collected after the initiation of rescue medication; the result will be a sensitivity analysis that uses a hypothetical strategy approach to the intercurrent even of initiation of rescue medication. A detailed plan for sensitivity/ supplemental analyses regarding potential intercurrent events including how to handle the data impacted by COVID19, will be provided in the statistical analysis plan.

9.6.1.4 Secondary Efficacy Endpoint Analyses

The key secondary endpoint will be the proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52 and will be analyzed using a logistic regression model with treatment group and stratified by factors used for stratifying the randomization. The logistic model will provide odds ratio, its 90% CI and p-value for comparing each fipaxalparant (HZN-825) group with the placebo group. Statistical significance for the key secondary endpoint will only be concluded if statistical significance is achieved for the primary efficacy endpoint.

Changes from Baseline in 6MWT, K-BILD, L-IPF, and LCQ scores will be analyzed analogously to the primary efficacy endpoints. Survival analysis will be used for the time-to-event endpoints, including time to the first onset of the composite endpoint and the time to the first hospitalization due to respiratory distress. A Cox proportional hazard model stratified like the previous logistic model with treatment group will provide hazard ratio, its 90% CI and p-value to compare each fipaxalparant (HZN-825) group with the placebo group.

9.6.1.5 Exploratory Endpoint Analyses

Exploratory endpoints will be summarized at each time point. The statistical methods for comparisons of each dose regimen of fipaxalparant (HZN-825) to placebo will be analogous to the methods for comparisons of primary and secondary efficacy endpoints. Correlation analysis will be used to assess the relationship between the percent change from Baseline in FVC % predicted and the percent change from Baseline in lung fibrosis scores at Week 52.

9.6.1.6 Safety and Tolerability Analyses

All subjects who receive at least 1 dose or partial dose of trial drug will be included in safety and tolerability analyses. Subjects who receive treatment other than that to which they were randomized will be included in summaries with the treatment received. Subjects who receive more than 1 treatment will be listed separately and included in summaries with the treatment received most frequently.

The number and percentage of subjects reporting at least 1 TEAE, SAE, AESI, and TEAE resulting in premature discontinuation of trial drug for each unique System Organ Class (SOC) and Preferred Term will be summarized. AE rates (events per patient-year of follow-up during dosing) will also be summarized to account for the different treatment durations. TEAEs and SAEs will also be summarized by severity and relationship to trial drug as assessed by the Investigator. Grade 3 and above TEAEs will also be summarized for each unique SOC and Preferred Term. Orthostatic hypotension is prospectively defined as an AESI and will be summarized separately.

Summary statistics will be used for laboratory values, vital signs, ECG results, and use of concomitant medications.

No inferential statistics are planned for any safety endpoint.

9.6.1.7 Pharmacokinetic Analyses

PK data will be analyzed using the PK analysis set. Plasma concentrations of fipaxalparant (HZN-825) will be summarized descriptively, including arithmetic means, standard deviations, geometric means, coefficients of variation, medians, first and third quartiles and ranges by treatment group and by time point. Population PK analysis may be performed.

9.6.1.8 Interim Analysis

An interim analysis of the primary efficacy endpoint will be conducted using unblinded data after [redacted]
This analysis will have 2 potential outcomes:

- If neither dose regimen of fipaxalparant (HZN-825) shows better efficacy compared to placebo with an acceptable safety profile, the trial will be discontinued for futility.
- If 1 or both dose regimens of fipaxalparant (HZN-825) show better efficacy compared to placebo with an acceptable safety profile, the trial will continue with no changes.

The futility analysis will not be used to make a positive determination of efficacy to stop the trial.

Conditional power will be used to determine which of the options is chosen, with a conditional power of ≥10% required for at least 1 dose regimen to continue the trial. Other statistics, such as Bayesian statistics, may also be used for the futility analysis and dose selection.

To support the dose selection and as part of the Week 28 unblinded interim analysis, the FVC % predicted change from Baseline at Week 28 will be evaluated in subjects who were randomized with concomitant standard-of-care treatment at Baseline. Approximately 60 subjects in the standard-of-care stratum with 28 weeks of data (approximately 20 subjects per arm) will be included. The positive signal in the FVC % predicted change from Baseline at Week 28 and related results in standard-of-care subjects will support the dose selection and future trial design.

Additionally, safety will be assessed, and an fipaxalparant (HZN-825) dose regimen that has an unacceptable safety profile will be discontinued and subjects assigned to that dose regimen would be assigned to the other dose regimen for the remainder of the trial, if the other dose regimen continues.

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.

9.6.1.9 Multiple Comparisons

The overall statistical level is α=0.10 (2-sided). Because 2 dose regimens of fipaxalparant (HZN-825) will be compared to placebo, a hierarchical testing procedure will be used for multiple comparisons. Therefore, α=0.10 (2-sided) will be used in the final 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 fipaxalparant (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.

9.6.2 Extension Phase

9.6.2.1 Endpoints

Two types of Baseline are defined for the Extension Phase:

- OLE Baseline, defined as the latest measurement prior to the first dose of fipaxalparant (HZN-825) in Extension Phase
- Fipaxalparant (HZN-825) Baseline, defined as the latest measurement prior to the first dose of fipaxalparant (HZN-825) in either the Core Phase or the Extension Phase. For subjects who received placebo in the Core Phase, OLE Baseline will be the same as fipaxalparant (HZN-825) Baseline.

9.6.2.1.1 Primary Efficacy Endpoint

The primary endpoint is the change from both Baselines in FVC % predicted at Week 104.

9.6.2.1.2 Safety and Tolerability Endpoints

- Incidence of TEAEs and the AESI (orthostatic hypotension) in the Extension Phase
- Concomitant medication use in the Extension Phase
- Change from Trial Baseline in vital signs in the Extension Phase
- Change from Trial Baseline in 12-lead ECG measurements in the Extension Phase
- Change from Trial Baseline in clinical safety laboratory test results in the Extension Phase

9.6.2.1.3 Exploratory Endpoints

- Change from both Baselines in proportion of subjects with decline in FVC % predicted ≥10% at Week 104
- Change from both Baselines in the 6MWT results to Week 104
- Change from both Baselines in K-BILD scores to Week 104
- Change from both Baselines in L-IPF scores to Week 104
- Change from both Baselines in LCQ scores to Week 104
- [redacted]
- Time to first hospitalization due to respiratory distress from fipaxalparant (HZN-825) Baseline up to Week 104
- Time to first onset of the composite endpoint of PFS from fipaxalparant (HZN-825) Baseline up to Week 104, where progression includes decline in FVC % predicted ≥10% from Baseline or death
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- Time to death due to respiratory deterioration from fipaxalparant (HZN-825) Baseline up to Week 104
- [redacted]
- [redacted]

9.6.2.1.4 Exploratory PK Endpoints

- Pre- and post-dose concentrations of fipaxalparant (HZN-825) in the Extension Phase

9.6.2.2 Analysis Sets

Three analysis sets will be defined for the Extension Phase of the trial.

- The FAS will include all subjects who entered and received at least 1 dose or partial dose of fipaxalparant (HZN-825) in the Extension Phase. This will be the analysis set used for efficacy data analyses; subjects will be analyzed according to the treatment group to which they were randomized in the Core Phase and combined into an 'overall' group.
- The safety analysis set will include all subjects who receive at least 1 dose or partial dose of fipaxalparant (HZN-825) in the Extension Phase. Subjects in this analysis set will be

analyzed according to the group determined by the treatment the subject received in the Core Phase and combined into an 'overall' group.

- The PK analysis set will include all subjects who received at least 1 dose or partial dose of fipaxalparant (HZN-825) and have at least 1 PK sample post fipaxalparant (HZN-825) treatment in the Extension Phase.

9.6.2.3 Efficacy Endpoint Analysis

All efficacy endpoints will be summarized for the FAS using descriptive statistics, presented by the treatment group subjects were randomly assigned to in the Core Phase and overall.

A 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 may 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 52 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.

Exploratory endpoints will be summarized at each time point. Change from Baseline will be evaluated separately for each of the defined Baselines.

9.6.2.4 Safety and Tolerability Analyses

All safety endpoints will be summarized for the safety analysis set in the Extension Phase using descriptive statistics.

The number and percentage of subjects reporting at least 1 TEAE, SAE, AESI and TEAE resulting in premature discontinuation of fipaxalparant (HZN-825) will be summarized by each unique SOC and Preferred Term. AE rates (events per patient-year of follow-up during dosing) will also be summarized to account for the different treatment durations. TEAEs and SAEs will also be summarized by maximum severity and relationship to fipaxalparant (HZN-825), as assessed by the Investigator. Grade 3 and above TEAEs will also be summarized for each unique SOC and Preferred Term.

The number and percentage of subjects using concomitant medications will be summarized by Anatomical Therapeutic Chemical Level 4 term and Preferred Term.

Laboratory values and change from OLE Baseline and fipaxalparant (HZN-825) Baseline will be summarized by visit using descriptive statistics. The laboratory assessment will be categorized as low, normal or high based on normal ranges. Shift tables using categories of low, normal and high from each Baseline to each visit in the Extension Phase will be summarized. If toxicity grading is available, then those grades will also be used for shift table summaries.

Descriptive summaries of observed and change from OLE Baseline and fipaxalparant (HZN-825) Baseline will be presented for each vital sign parameter by visit. A shift table for vital signs by visit will be provided.

ECG results will be summarized for each visit in the Extension Phase.

9.6.2.5 Pharmacokinetic Analyses

PK data will be analyzed using the PK analysis set. Plasma concentrations of fipaxalparant (HZN-825) will be summarized descriptively, including arithmetic means, standard deviations, geometric means, coefficients of variation, medians, first and third quartiles and ranges by treatment group in the Core Phase and by time point. Population PK analysis may be performed.

9.6.3 Sample Size and Power Considerations

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 fipaxalparant (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.

9.7 Changes in the Conduct of the Trial

If any modifications in the experimental design, dosages, parameters, subject selection or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before any such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approved from the appropriate external review bodies.

The Investigator or other health professional in attendance must contact the Sponsor as soon as possible. All protocol deviations and the reasons for such deviations **must** be documented into the electronic database. In the event of a protocol deviation, the Investigator and Sponsor's Medical Monitor will determine whether the subject should continue to participate in the trial.

The Sponsor has a legal responsibility to report fully to regulatory authorities all results of administration of investigational drugs to humans. No investigational procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the external review bodies and Sponsor.

10 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

The Investigator must maintain adequate and accurate records to document fully the conduct of the trial and to ensure that trial data can be subsequently verified. These documents should be classified in 2 separate categories: (1) Investigator trial file and (2) subject clinical source documents that corroborate data collected in the eCRFs. Subject clinical source documents would include, as applicable, original hospital/clinic subject records; physicians and nurses' notes; appointment book; original laboratory, ECG, echocardiogram, electroencephalogram, radiology, pathology, and special assessment reports; dispensing records; signed ICFs; consultant letters; and subject Screening and enrollment logs.

In order to comply with regulatory requirements, it is the policy of the Sponsor that, at a minimum, the following be documented in source documents at the trial center:

- Medical history/physical condition and diagnosis of the subject before involvement in the trial sufficient to verify that the subject meets protocol entry criteria.
- Trial number, assigned subject number and verification that written informed consent was obtained (each recorded in dated and signed progress notes).
- Progress notes or for each subject visit (each dated and signed).
- Records of each trial visit including each trial assessment and the identity of the staff member performing the assessment.
- Trial drug dispensing and return.
- Review by the Investigator or qualified personnel on the 1572 of laboratory test results.
- AEs (start and stop date, description, relationship to trial drug, action taken and resolution).
- Investigator or Sub-Investigator's signed assessment of each AE.
- Concomitant medications (start and stop dates, reason for use).
- Condition of subject upon completion of, or premature discontinuation from, the trial.

11 CASE REPORT FORMS

An eCRF is required for every subject who signs the ICF. Required data must be entered on the eCRF within the required time period, which will be outlined within each site agreement, after data collection or the availability of test results. Separate source records are required to support all eCRF entries.

The Investigator will ensure that the eCRFs are accurate, complete, legible and timely and will review and provide an electronic signature for the eCRF according to the standard operating procedure of the Data Management System. Final eCRFs will be provided to the Investigator and Sponsor by Data Management.

12 TRIAL MONITORING

The Investigator will ensure that the trial is conducted in accordance with all regulations governing the protection of human subjects and will adhere to the basic principles of GCP as outlined in Title 21 of the CFR, Part 312, Subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, Part 50, "Protection of Human Subjects"; 21 CFR, Part 56, "Institutional Review Boards"; 21 CFR, Part 54 "Financial Disclosure by Clinical Investigators"; and the ICH guideline entitled "Good Clinical Practice: Consolidated Guidance." Additionally, this trial will be conducted in compliance with the Declaration of Helsinki and with all local laws and regulations.

The Investigator will ensure that all work and services described in or associated with this protocol are conducted in accordance with the investigational plan, applicable regulations and the highest standards of medical and clinical research practice. The Investigator will provide copies of the trial protocol and Investigator's Brochure to all Sub-Investigators, pharmacists and other staff responsible for trial conduct.

All aspects of the trial will be monitored by qualified individuals designated by the Sponsor. The Sponsor will ensure that the trial is monitored adequately in accordance with GCP guidelines.

Prior to initiation of the trial, the Sponsor's representatives will review with trial center personnel information regarding the investigational drug, protocol requirements, monitoring requirements, and reporting of SAEs.

At intervals during the trial, as well as after the completion of subject enrollment, the trial center will be monitored by the Sponsor or designee for compliance. During these visits, the monitor will discuss trial progress, verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the eCRF (source data verification); oversee the resolution of outstanding data discrepancies; and check on various aspects of trial conduct (e.g., drug accountability, sample storage). The Investigator agrees to allow unblinded monitors access to the clinical supplies, dispensing and storage areas and clinical records of the trial subjects and, if requested, agrees to assist the monitors. The Investigator must cooperate with the monitors to ensure that any problems detected in the course of these monitoring visits are resolved.

A secondary audit may be conducted by Quality Assurance designated by the Sponsor. The Investigator will be informed if this is to take place and advised as to the nature of the audit. Representatives of the FDA and/or representatives of other regulatory authorities may also conduct an inspection of the trial at the investigative site. If informed of such an inspection, the Investigator should notify the Sponsor immediately.

Every effort will be made to maintain the anonymity and confidentiality of subjects participating in this clinical trial. However, because of the investigational nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, its designated agents and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this trial and to

have direct access to inspect, for purposes of verification, the hospital or clinical records of all subjects enrolled in this trial. A statement to this effect should be included in the ICF.

Serious Breach

Suspected Serious Breaches must be reported to the study team (e.g., Clinical Monitor) or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness.

A Serious Breach is a breach of any of the following:

- GCP
- the clinical trial protocol
- an applicable regulation

That is likely to impact to a significant degree either of the following:

- the safety, physical, or mental integrity and the rights of the participant
- the reliability and robustness of the data and the scientific value of the trial

13 DATA MANAGEMENT

Data will be entered into a clinical database as specified in the Data Management Plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. Data will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be communicated to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database and all corrections will be documented in an audit trail.

The coding of an AE, medical history and concomitant medication terms will be performed by a qualified medical coder and reviewed and approved by the Sponsor. Concomitant medications will be coded using the World Health Organization Drug Dictionary and AE/medical history/surgery/non-drug therapy terms will be coded using the Medical Dictionary for Regulatory Activities.

14 RETENTION OF RECORDS

No trial documents at the trial site should be destroyed without prior written agreement between the Sponsor and the Investigator. All subjects' medical records, the Investigator's copy of the eCRF, other supporting data, records of drug dispensing and accountability, signed ICFs, external review bodies correspondence and correspondence with the Sponsor must be kept by the Investigator for at least 2 years and as required by the local law following the date of the last approval of a marketing application in an ICH region (including the US) and until there are no pending or contemplated marketing applications in any other ICH region. If an application is not filed or not approved for the indication under study, all trial-related files must be retained for at least 2 years following the date of discontinuation of the clinical development program for fipaxalparant (HZN-825) and for a period in compliance with all federal, state and local regulations. The Sponsor must be notified prior to the disposal of any trial-related files. If the Investigator leaves the practice or institution during the required retention period, it is important that arrangements be made for continued record retention. In that event, the records generally will be retained at the institution at which the trial was conducted.

15 PUBLICATION

To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts and electronic communications) as detailed in the Clinical Trial Agreement.

Independent publications of results, including unfavorable results, will be submitted to applicable databases within the required timeframe.

16 REFERENCES

Allanore Y, Distler O, Jagerschmidt A, et al. Lysophosphatidic acid receptor 1 antagonist SAR100842 for patients with diffuse cutaneous systemic sclerosis. Arthritis Rheumatol. 2018;70:1634-43.

American Thoracic Society. Idiopathic pulmonary fibrosis: Diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000;161:646-64.

ATS Guidelines. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7. Erratum in: Am J Respir Crit Care Med. 2016;193(10):1185.

Barratt SL, Creamer A, Hayton C, Chaudhuri N. Idiopathic pulmonary fibrosis (IPF): an overview. J Clin Med. 2018;7(8):201.

Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MDL, Pavord DI. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58:339-43.

Black KE, Berdyshev E, Bain G, et al. Autotaxin activity increases locally following lung injury, but is not required for pulmonary lysophosphatidic acid production or fibrosis. FASEB J. 2016;30:2435-50.

Blanqué R, Desroy N, Dupont S, et al. Pharmacological profile and efficacy of GLPG1690, a novel ATX inhibitor for COPD treatment. Eur Res Society Poster 2015. Available online at www.glpg.com.

Cabello-Verrugio C, Cordova G, Vial C, Zuniga LM, Brandan E. Connective tissue growth factor induction by lysophosphatidic acid requires transactivation of transforming growth factor type beta receptors and the JNK pathway. Cell Signal. 2011;23(2):449-57.

Chun J, Goetzl EJ, Hla T, et al. International Union of Pharmacology. XXXIV. Lysophospholipid receptor nomenclature. Pharmacol Rev. 2002;54(2):265-9.

Collard HR, Ryerson CJ, Corte TJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. an international working group report. Am J Respir Crit Care Med. 2016;194(3):265-75.

Desroy N, Housseman C, Bock X, et al. Discovery of 2-[[2-Ethyl-6-[4-[2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]piperazin-1-yl]-8-methylimidazo[1,2-a]pyridin-3-yl]methylamino]-4-(4-fluorophenyl)thiazole-5-carbonitrile (GLPG1690), a first-in-class autotaxin inhibitor undergoing clinical evaluation for the treatment of idiopathic pulmonary fibrosis. J Med Chem. 2017;60(9):3580-90.

Diamantopoulos A, Wright E, Vlahopoulou K, Cornic L, Schoof N, Maher TM. The burden of illness of idiopathic pulmonary fibrosis: a comprehensive evidence review. Pharmacoeconomics. 2018;36:779-807.

ESBRIET® (pirfenidone). Full Prescribing Information. Revision date: 7/2019.

Fukushima N, Ishii I, Contos JJ, Weiner JA, Chun J. Lysophospholipid receptors. Annu Rev Pharmacol Toxicol. 2001;41:507-34.

Funke M, Zhao Z, Xu Y, Chun K, Tager M. The lysophosphatidic acid receptor LPA1 promotes epithelial cell apoptosis after lung injury. Am J Respir Cell Mol Biol. 2012;46(3):355-64.

Geraldo LHM, de Sampaio Spohr TCL, do Amaral RF, et al. Role of lysophosphatidic acid and its receptors in health and disease: novel therapeutic strategies. Signal Transduct Target Ther. 2021;6:45.

Graham BL, Brusasco V, Burgos F, et al. Executive Summary: 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017;49:16E0016.

Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200:e70-e88.

Gribbin J, Hubbard RB, le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006;61:980-5.

Hopkins RB, Burke N, Fell C, Dion G, Kolb M. Epidemiology and survival of idiopathic pulmonary fibrosis from national data in Canada. Eur Respir J. 2016;48:187-95.

Human Albumin. Transfus Med Hemother. 2009;36:399-407.

Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: A systematic review. Eur Respir J. 2015;46:795-806.

Idzko M, Laut M, Panther E, et al. Lysophosphatidic acid induces chemotaxis, oxygen radical production, CD11b up-regulation, Ca2+ mobilization, and actin reorganization in human oesinophils via pertussis toxin-sensitive G proteins. J Immunol. 2004;172(7):4480-5.

Kim J, Keys JR, Eckhart AD. Vascular smooth muscle migration and proliferation in response to lysophosphatidic acid (LPA) is mediated by LPA receptors coupling to Gq. Cell Signal. 2006;18(10):1695-701.

King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083-92.

Knowlden S, Georas SN. The autotaxin-LPA axis emerges as a novel regulator of lymphocyte homing and inflammation. J Immunol. 2014;192(3):851-7.

Kreuter M, Polke M, Walsh SLF, et al. Acute exacerbation of idiopathic pulmonary fibrosis: international survey and call for harmonisation. Eur Respir J. 2020;55(4):1901760.

Lancaster LH. Utility of the six-minute walk test in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med. 2018;13;13:45.

Lancaster LH, de Andrade JA, Zibrak JD, et al. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. Eur Respir Rev. 2017;26:170057.

Ledein L, Léger B, Dees C, et al. Translational engagement of LPA_1 receptor in skin fibrosis: from dermal fibroblasts of patients with scleroderma to Tsk1 mouse. Br J Pharmacol. 2020;177:4296-309.

Maher TM, van der Aar EM, Van de Steen O, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial. Lancet Respir Med. 2018;6(8):627-35.

Nakamura K, Igarashi K, Ide K, et al. Validation of an autotaxin enzyme immunoassay in human serum samples and its application to hypoalbuminemia differentiation. Clin Chim Acta. 2008;388(1-2):51-8.

Nakanaga K, Hama K, Aoki J. Autotaxin—an LPA producing enzyme with diverse functions. J Biochem. 2010;148(1):13-24.

Nathan SD, Costabel U, Albera C, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment. Respir Med. 2019;153:44-51.

Navaratnam V, Fleming KM, West J, et al. The rising incidence of idiopathic pulmonary fibrosis in the U.K. Thorax. 2011;66:462-7.

Ninou I, Magkrioti C, Aidinis V. Autotaxin in pathophysiology and pulmonary fibrosis. Front Med (Lausanne). 2018;5:180.

OFEV® (nintedanib capsules). Full Prescribing Information. Revision date: 10/2020.

Oikonomou N, Mouratis M-A, Tzouvelekis A, et al. Pulmonary autotaxin expression contributes to the pathogenesis of pulmonary fibrosis. Am J Respir Cell Mol Biol. 2012;47(5):566-74.

Oldham WM, Hamm HE. Heterotrimeric G protein activation by G-protein-couples receptors. Nat Rev Mol Cell Biol. 2008;9:60-71.

Palmer SM, Synder L, Todd JL, et al. Randomized, double-blind, placebo-controlled, phase 2 trial of BMS-986020, a lysophosphatidic acid receptor antagonist for the treatment of idiopathic pulmonary fibrosis. Chest. 2018;154:1061-9.

Panther E, Idzko M, Corinti S, et al. The influence of lysophosphatidic acid on the functions of human dendritic cells. J Immunol. 2002;169:4129-35.

Patel AS, Siegert RJ, Brignall K, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax. 2012;67:804-10.

Pradère JP, Klein J, Grès S, et al. LPA_1 receptor activation promotes renal interstitial fibrosis. J Am Soc Nephrol. 2007;18:3110-8.

Qian Y, Hamilton M, Sidduri A, et al. discovery of highly selective and orally active lysophosphatidic acid receptor-1 antagonists with potent activity on human lung fibroblasts. J Med Chem. 2012;55(17):7920-39.

Raghu G, Chen SY, Yeh WS, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001–11. Lancet Respir Med. 2014;2:566-72.

Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788-824.

Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Car Med. 2018;198:e44-68.

Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205(9):e18-47.

Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Car Med. 2015;192:e3-19.

Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071-82.

Schober A, Siess W. Lysophosphatidic acid in atherosclerotic diseases. Br J Pharmacol. 2012;167(3):465-82.

Sinha A, Patel AS, Siegert RJ, et al. The King's Brief Interstitial Lung Disease (KBILD) questionnaire: an updated minimal clinically important difference. BMJ Open Respir Res. 2019;6:e000363.

Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. Adv Ther. 2018;35:724-36.

Swaney JS, Chapman C, Correa LD, et al. A novel, orally active LPA_1 receptor antagonist inhibits lung fibrosis in the mouse bleomycin model. Br J Pharmacol. 2010;160:1699-713.

Swigris JJ, Andrae DA, Churney T, et al. Development and initial validation analyses of the Living with Idiopathic Pulmonary Fibrosis Questionnaire. Am J Respir Crit Care Med. 2020;202:1689-97.

Swigris JJ, Broan KK, Behr J, et al. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. Respir Med. 2010;104:296-304.

Tager AM, LaCamera P, Shea BS, et al. The lysophosphatidic acid receptor LPA_1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. Nat Med. 2008;14(1):45-54.

Takuma Y, Takuma N, Sugimoto N. The Edg family G protein-coupled receptors for lysophospholipids: their signaling properties and biological activities. J Biochem. 2002;131(6):767-71.

Tanaka M, Okudaira S, Kishi Y, et al. Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid. J Biol Chem. 2006;281(35):25822-30.

Tang N, Zhao Y, Feng R, et al. Lysophosphatidic acid accelerates lung fibrosis by inducing differentiation of mesenchymal stem cells into myofibroblasts. J Cell Mol Med. 2014;18(1):156-69.

Tokumura A, Carbone LD, Yoshioka Y, et al. Elevated serum levels of arachidonoyl-lysophosphatidic acid and sphingosine 1-phosphate in systemic sclerosis. Int J Med Sci. 2009;6:168-76.

Tomioka H, Imanaka K, Hashimoto K, Iwasaki H. Health-related quality of life in patients with idiopathic pulmonary fibrosis--cross-sectional and longitudinal study. Intern Med. 2007;46:1533-42.

Tsuda S, Okudaira S, Moriya-Ito K, et al. Cyclic phosphatidic acid is produced by autotaxin in blood. J Biol Chem. 2006;281(36):26081-8.

US Department of Health and Human Services, Food and Drug Administration. Drug-induced liver injury: premarketing clinical evaluation. July 2009.

Valdes-Rives SA, González-Arenas A. Autotaxin-lysophosphatidic acid: from inflammation to cancer development. Mediators Inflamm. 2017:9173090.

van der Aar EM, Heckmann B, Blanque R, et al. Pharmacological profile and efficacy of GLPG1690, a novel autotaxin inhibitor for the treatment of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2020;201:A4532.

van Meeteren LA, Ruurs P, Stortelers C, et al. Autotaxin, a secreted lysophospholipase D, is essential for blood vessel formation during development. Mol Cell Biol. 2006;26:5015-22.

Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220-33.

Woodworth T, Furst DE, Alten R, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v2.0. J Rheumatol. 2007;34(6):1401-14.

Yin Z, Tong Y, Zhu H, Watsky MA. CLC-3 is required for LPA-activated Cl- current activity and fibroblasts to myofibroblasts differentiation. Am J Physiol Cell Physiol. 2008;294(2):535-42.

Yung YC, Stoddard NC, Chun J. LPA receptor signaling: pharmacology, physiology, and pathophysiology. J Lipid Res. 2014;55:1192-214.

Zhao Y, Natarajan V. Lysophosphatidic acid (LPA) and its receptors: role in airway inflammation and remodeling. Biochim Biophys Acta. 2013;1831(1):86-92.

17 APPENDICES

Versions of the assessment instruments are provided in the appendices as examples based on the versions available at the time of protocol publication and may differ from the assessment instruments actually administered in the trial in the event that additional validated versions become available.

17.1 Administrative Appendix

This appendix provides names and contact information for the trial administrative structure. The external review bodies must be notified of changes that are made to this section, but external review bodies review or approval of these changes is not required. Changes made in this section will be dated but will not be assigned a protocol amendment number.

Medical Monitor	[redacted] MBBS, MD Senior Medical Director, Clinical Development (Rare Disease) Horizon Therapeutics USA., Inc. 1 Horizon Way Deerfield, IL 60015 Mobile telephone number: [redacted] Email: [redacted]
Sponsor Representative	[redacted] Associate Director, Clinical Operations Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015 Business telephone number: [redacted] Email: [redacted]

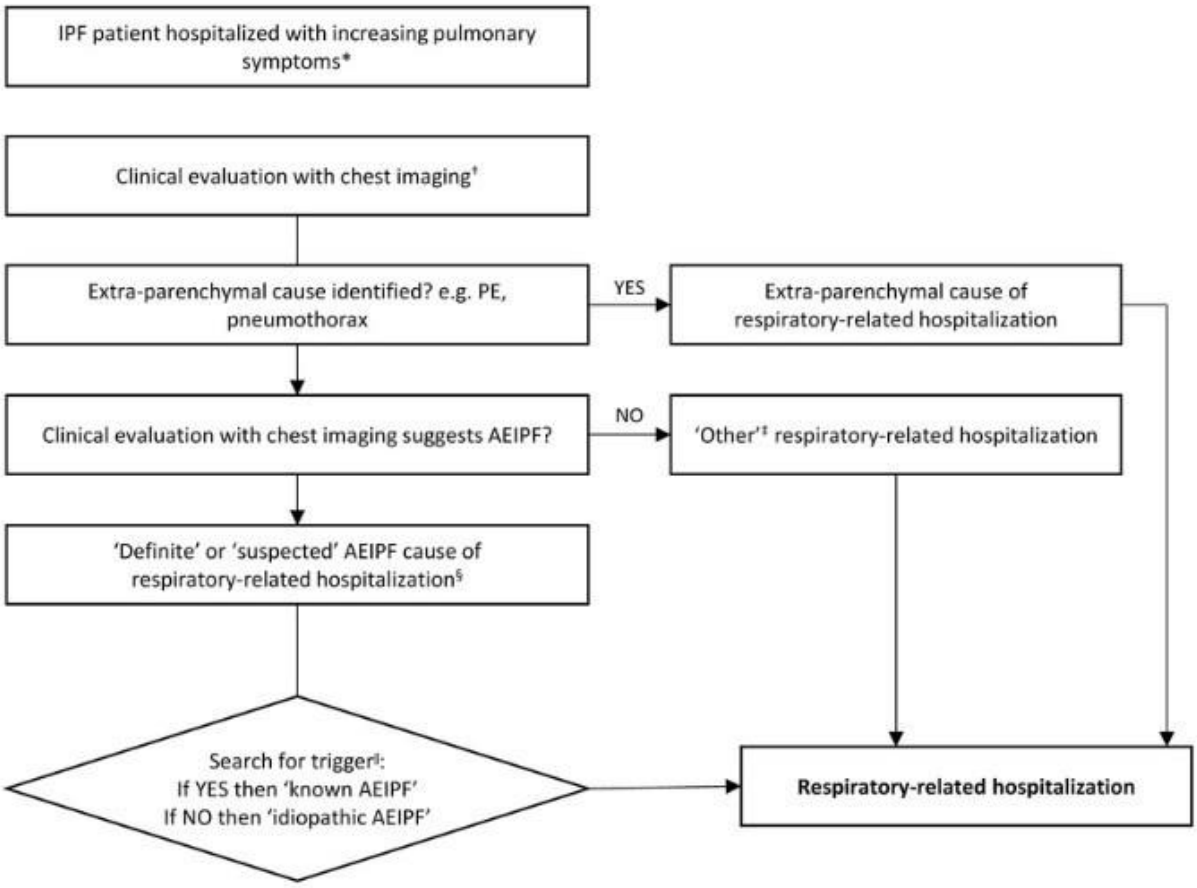
17.2 Hospitalization Due to Respiratory Distress

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.

Clinical information for potential hospitalization due to respiratory distress will be collected on a dedicated questionnaire. In addition, all relevant clinical data (summary on clinical course, signs and symptoms; laboratory, lung function and imaging results; and treatment provided) relating to the hospitalization will be collected and provided to an independent adjudication committee for review.

Clinical information related to potential respiratory related hospitalizations will be provided to an independent adjudication committee for review in accordance with the standardized algorithm proposed by Kreuter et al., 2020 (Figure 17.1). For additional details, refer to the adjudication committee charter.

Figure 17.1 Algorithm for Adjudication of Respiratory-related Hospitalization in Idiopathic Pulmonary Fibrosis



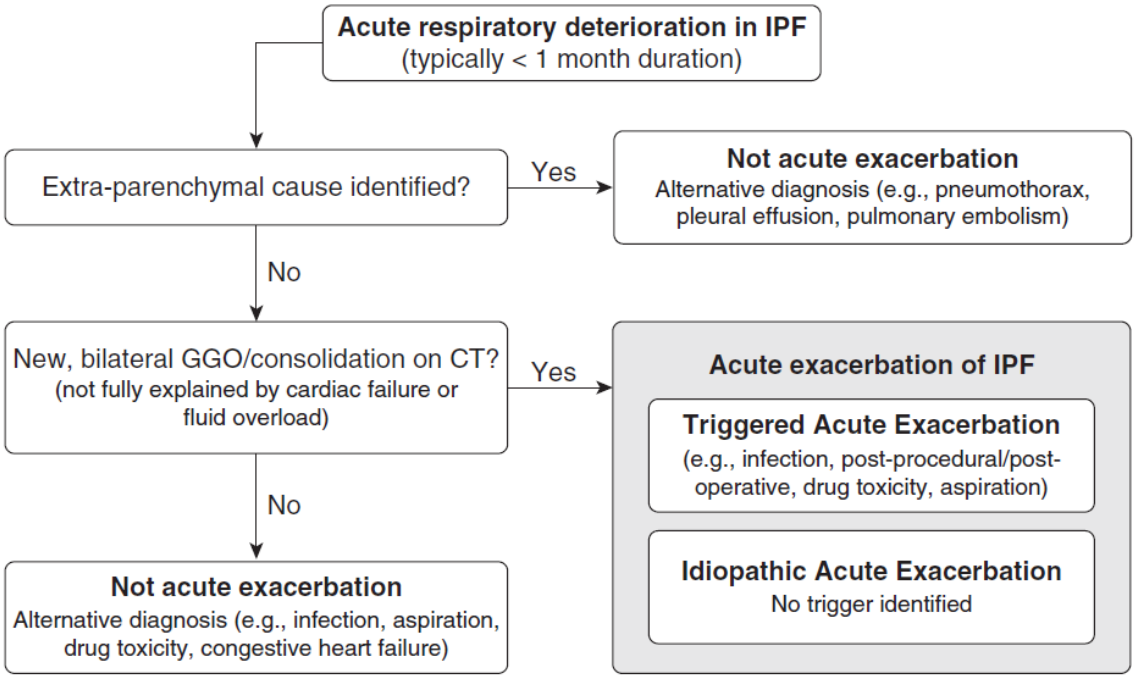
*Presenting to ER elective or non-elective. Elective (non-emergency) admission to hospital for lung transplantation is excluded.
†Non-enhanced thin section high-resolution computed tomography is the preferred form of chest imaging.
‡Specifically, rule out primary cardiac causes such as CCF, MI, arrhythmia. In the absence of significant LV dysfunction in a patient with IPF, right heart failure is considered a respiratory cause.
§Definite cases of AEIPF should be reserved for patients with radiological evidence of DAD. If not, then the case is suspected.
‖Exacerbations with identified triggers (infective, post-procedural or traumatic, drug-toxicity-related or aspiration-related) are classed as 'known AEIPF' exacerbations with no identified trigger are classed as 'idiopathic AEIPF'.
Note that for the sake of simplicity, 'extra-parenchymal' and 'other respiratory' are both considered respiratory causes of hospitalization, together with AEIPF ('definite' or 'suspected', in which both are either 'triggered' or 'idiopathic'). All other admissions are 'non-respiratory' and classed as such.
AE, acute exacerbation; CCF, congestive cardiac failure; DAD, diffuse alveolar damage; ER, emergency room; IPF, idiopathic pulmonary fibrosis; LV, left ventricular; MI, myocardial infarction; PE, pulmonary embolism.

17.3 IPF-related Acute Exacerbation

Clinical information for potential IPF-related acute exacerbations will be collected on a dedicated questionnaire. In addition, all relevant clinical data (summary on clinical course, signs and symptoms; laboratory, lung function and imaging results; and treatment provided) relating to the exacerbation will be collected and provided to an independent adjudication committee for review. The conceptual framework for evaluation of acute respiratory deterioration in IPF, as defined by Collard et al., 2016, is shown in Figure 17.2. Acute respiratory deterioration of IPF (defined as "typically, 1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural effusion) or parenchymal. Parenchymal

causes that demonstrate new bilateral ground-glass opacification/consolidation on computed tomography that is not fully explained by cardiac failure or fluid overload are categorized as acute exacerbations of IPF, regardless of the presence or absence of a known trigger (e.g., infection). Acute exacerbations are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found. For additional details, refer to the adjudication committee charter.

Figure 17.2 Conceptual Framework for Evaluation of Acute Respiratory Deterioration in IPF



Source: [Collard et al., 2016]
CT=computed tomography; GGO=ground-glass opacification; IPF=idiopathic pulmonary fibrosis

The revised definition and diagnostic criteria for acute exacerbation of IPF are shown in Table 17.1.

Table 17.1 Proposed Revised Definition and Diagnostic Criteria for Acute Exacerbation of IPF

Revised definition
An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality
Revised diagnostic criteria
• Previous or concurrent diagnosis of IPF* • Acute worsening or development of dyspnea typically <1 month in duration • Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern† • Deterioration not fully explained by cardiac failure or fluid overload

Source: [Collard et al., 2016]
IPF=idiopathic pulmonary fibrosis
Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet all 4 diagnostic criteria owing to missing computed tomography data should be termed "suspected acute exacerbations."
*If the diagnosis of IPF is not previously established, this criterion can be met by the presence of radiologic and/or histopathologic changes consistent with usual interstitial pneumonia pattern on the current evaluation.
†If no previous computed tomography is available, the qualifier "new" can be dropped.

17.4 Living with IPF

Symptoms Module

Instructions for Completing the Living with IPF (L-IPF) Symptoms Module

This questionnaire is designed to assess the symptoms you may have experienced from Idiopathic Pulmonary Fibrosis (IPF) over the last 24 hours.

Keep in mind:

- you are not being asked to compare yourself to anyone else
- you are not being asked to compare how you are now with any time in the past

---

Items 1-7: The first 7 items ask about your symptoms in relation to physical activities, some of which you may not have done in the **last 24 hours**. If you did not perform an activity, we would like to know whether it was because you did not have the opportunity to do it (for example, maybe your home doesn't have stairs, so you did not walk up a flight of stairs), or whether you avoided the activity because it was too difficult.

If you did the stated activity, then reflect on the last 24 hours, and consider whether, on average, doing the activity at your usual pace or intensity level made you short of breath—and if so, how much.

Note: If you normally use oxygen when you perform a given activity, then consider your response as if you were using supplemental oxygen.

For each question, please select the box that best describes your experience.

---

1. Did you walk up one flight of stairs in the last 24 hours?

Yes How short of breath did walking up one flight of stairs make you?

Not at all **0** **1** **2** **3** **4** Extremely

No I did not walk up one flight of stairs in the last 24 hours because:

A I avoided this activity because it was too difficult to perform

B Not applicable, because I did not want or have the opportunity to do it

2. **Over the last 24 hours, how short of breath have you been while sitting down, relaxing, reading, or watching TV?**

Not at all [0] [1] [2] [3] [4] Extremely

3. **Did you perform a grooming activity (e.g., brush teeth, shave, fix hair) in the last 24 hours?**

[Yes] How short of breath did grooming make you?

Not at all [0] [1] [2] [3] [4] Extremely

[No] I did not perform a grooming activity in the last 24 hours because:

[A] I avoided this activity because it was too difficult to perform

[B] Not applicable, because I did not want or have the opportunity to do it

4. **Did you walk outside on a level surface (approximately 150 feet/45 meters, or the distance of half a typical city block) in the last 24 hours?**

[Yes] How short of breath did walking outside on a level surface make you?

Not at all [0] [1] [2] [3] [4] Extremely

[No] I did not walk outside on a level surface in the last 24 hours because:

[A] I avoided this activity because it was too difficult to perform

[B] Not applicable, because I did not want or have the opportunity to do it

5. **Did you bathe or shower in the last 24 hours?**

[Yes] How short of breath did bathing or showering make you?

Not at all [0] [1] [2] [3] [4] Extremely

[No] I did not bathe or shower in the last 24 hours because:

[A] I avoided this activity because it was too difficult to perform

[B] Not applicable, because I did not want or have the opportunity to do it

6. Did you lift and carry a light load (e.g., less than 10 lbs) a short distance (e.g., from one room to another) in the last 24 hours?

Yes — How short of breath did lifting and carrying a light load a short distance make you?

Not at all 0 1 2 3 4 Extremely

No — I did not lift and carry a light load a short distance in the last 24 hours because:

A — I avoided this activity because it was too difficult to perform

B — Not applicable, because I did not want or have the opportunity to do it

7. Did you become short of breath in the last 24 hours?

Yes — How long did it take you to recover when you became short of breath?

No time at all 0 1 2 3 4 An extremely long time

No — Please continue to the next question

Items 8-12: These items primarily focus on your cough. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

8. Over the last 24 hours, how often did you cough?

Not at all 0 1 2 3 4 Constantly

If you chose "0", please skip to item 13.

9. Over the last 24 hours, how often did you cough when you took a deep breath?

Not at all 0 1 2 3 4 Constantly

10. Over the last 24 hours, how often did you cough when you exerted?

Not at all 0 1 2 3 4 Constantly

11. Over the last 24 hours, how often did you feel an annoying tickle in your throat?

Not at all | 0 | 1 | 2 | 3 | 4 | Constantly

12. Over the last 24 hours, how much did coughing have a negative effect on your energy?

No effect at all | 0 | 1 | 2 | 3 | 4 | A lot

Items 13-15: These items primarily focus on your energy level. Again, reflect on the last 24 hours as you consider where you are on the scale between the two statements.

13. Over the last 24 hours, how was your energy?

Extremely low | 0 | 1 | 2 | 3 | 4 | Excellent

14. Over the last 24 hours, of all that you wanted to get done, how much did you actually get done?

Nothing | 0 | 1 | 2 | 3 | 4 | Everything

15. Over the last 24 hours, how much energy did you have to do all the things you like to do?

No energy | 0 | 1 | 2 | 3 | 4 | A lot

Finally, we would like to ask you 5 questions about your supplemental oxygen use.

Oxygen Question 1. Do you ever use supplemental oxygen?
(Place an "X" in one box)

- [ ] Yes →→ proceed to Oxygen Question #2.
- [ ] No →→ You are finished. Skip Oxygen Questions 2-5

Oxygen Question 2. I use supplemental oxygen...
(Place an "X" in one box)

- [ ] A →→ **only when I sleep (answer Oxygen Question #3)**
- [ ] B →→ only when I perform a physical activity (such as exercising, walking or shopping) (answer Oxygen Question #4)
- [ ] C →→ **when I sleep or perform a physical activity (such as exercising, walking or shopping, but not at rest; answer Oxygen Questions #3 and #4)**
- [ ] D →→ all the time (answer Oxygen Questions #3-5)

Oxygen Question 3. When I sleep, I most often use an oxygen flow rate of ___L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Oxygen Question 4. When I perform a physical activity (such as exercising, walking or shopping), I most often use an oxygen flow rate of_____L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Oxygen Question 5. At rest, I most often use an oxygen flow rate of____L/min.
(Place an "X" in one box)

0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5	6	7	8	9	10	11	12	>12
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

>>The end. Thank you for taking the time to complete the L-IPF Symptoms Module.<<

Impacts Module

Instructions for Completing the Living with IPF (L-IPF) Impacts Module

The goal of this questionnaire is to determine how Idiopathic Pulmonary Fibrosis affects your quality of life.

Quality of life refers to your perceptions of your overall position in life in relation to:

- your goals and expectations
- your standards and values
- your concerns and judgments

Among other things, quality of life encompasses:

- your physical health (conditions/diseases, symptoms, therapies)
- your psychological state (outlook, emotional well-being)
- your level of independence
- the relationships you have with pertinent features of your environment

Reflect on your life: has Idiopathic Pulmonary Fibrosis affected your quality of life?
As you respond to the items, reflect on your physical health, how you have been functioning, your psychological state, how you have been feeling, your level of independence, what you have done, and where you have gone over the last 7 days.

Items 1-15: For these items, reflect on the **last 7 days** as you consider where you are on the 0-4 scale between the two statements.

On average, over the last 7 days…

1. **How much did shortness of breath prevent you from doing things you wanted to do?**

   Not at all | 0 | 1 | 2 | 3 | 4 | Extremely

2. **How much did fear of becoming too short of breath limit your physical exertion?**

   Not at all | 0 | 1 | 2 | 3 | 4 | Extremely

3. **How was your stamina when you exerted physically?**

   Extremely poor | 0 | 1 | 2 | 3 | 4 | Excellent

4. **How frustrated were you by the time it took you to complete a physical activity?**

   Not at all | 0 | 1 | 2 | 3 | 4 | Extremely

5. **How frustrated were you by your need to rest during or after completing a physical activity?**

   Not at all | 0 | 1 | 2 | 3 | 4 | Extremely

On average, over the last 7 days…

6. How much did coughing embarrass you?

Not at all 0 1 2 3 4 Extremely

7. How much did coughing frustrate you?

Not at all 0 1 2 3 4 Extremely

8. How much did coughing interrupt your conversations (in person or on the phone)?

Not at all 0 1 2 3 4 Extremely

9. How frightening was your coughing to you?

Not at all 0 1 2 3 4 Extremely

10. How much was your cough a problem for you?

Not at all 0 1 2 3 4 Extremely

11. How much hassle or inconvenience has IPF caused you in your day-to-day life?

None 0 1 2 3 4 A lot

12. How much did you have to rest in the middle of doing a simple chore inside the house?

Not at all 0 1 2 3 4 A lot

13. How much did you have to pace yourself to make it through the day?

Not at all 0 1 2 3 4 A lot

14. How much time did it take to get yourself ready to leave the house?

Very little time 0 1 2 3 4 Extremely long time

15. How much were you forced to depend on other people to do things for you?

Not at all 0 1 2 3 4 A lot

For Items 16-18: Think broadly about your shortness of breath, cough and energy level over the last 7 days. Have these symptoms affected how you have felt physically? Psychologically? Have they disrupted your life? Or limited you in terms of what you would like to do or how you would like to do it? Now, please respond to Items 16-18.

On average, over the last 7 days…

16. How has shortness of breath affected your quality of life?

Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect

17. How much has your cough affected your quality of life?

Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect

18. How much has your energy level affected your quality of life?

Made my quality of life extremely poor | 0 | 1 | 2 | 3 | 4 | No negative effect

For these last two, Items 19 and 20: Think broadly again about whether IPF has affected you and your quality of life over the last 7 days. Reflect on your symptoms and other aspects of your physical health, how you have been functioning, your psychological state, how you have been feeling, your level of independence, what you have done, and where you have gone over the last 7 days.

On average, over the last 7 days…

19. How have you felt in terms of physical health?

Extremely poor | 0 | 1 | 2 | 3 | 4 | Excellent

20. How has your quality of life been?

Extremely poor | 0 | 1 | 2 | 3 | 4 | Excellent

>> The end. Thank you for taking the time to complete the L-IPF Impacts Module. <<

17.5 King's Brief Interstitial Lung Disease Questionnaire

The King's Brief Interstitial Lung Disease Questionnaire (K-BILD)©2011

This questionnaire is designed to assess the impact of your lung disease on various aspects of your life. Please circle the response that best applies to you for each question

1. In the last 2 weeks, I have been breathless climbing stairs or walking up an incline or hill.						
1. Every time	2. Most times	3. Several Times	4. Some times	5. Occasionally	6. Rarely	7. Never
2. In the last 2 weeks, because of my lung condition, my chest has felt tight.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
3. In the last 2 weeks have you worried about the seriousness of your lung complaint?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
4. In the last 2 weeks have you avoided doing things that make you breathless?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
5. In the last 2 weeks have you felt in control of your lung condition?						
1. None of the time	2. Hardly any of the time	3. A little of the time	4. Some of the time	5. A good bit of the time	6. Most of the time	7. All of the time
6. In the last 2 weeks, has your lung complaint made you feel fed up or down in the dumps?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
7. In the last 2 weeks, I have felt the urge to breathe, also known as 'air hunger'.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
8. In the last 2 weeks, my lung condition has made me feel anxious.						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
9. In the last 2 weeks, how often have you experienced 'wheeze' or whistling sounds from your chest?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
10. In the last 2 weeks, how much of the time have you felt your lung disease is getting worse?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
11. In the last 2 weeks has your lung condition interfered with your job or other daily tasks?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
12. In the last 2 weeks have you expected your lung complaint to get worse?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
13. In the last 2 weeks, how much has your lung condition limited you carrying things, for example, groceries?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
14. In the last 2 weeks, has your lung condition made you think more about the end of your life?						
1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. Hardly any of the time	7. None of the time
15. Are you financially worse off because of your lung condition?						
1. A significant amount	2. A large amount	3. A considerable amount	4.A reasonable amount	5. A small amount	6. Hardly at all	7. Not at all

Source: [Patel et al., 2012]

17.6 Leicester Cough Questionnaire

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Some times	Occasionally	Rarely	Never

3. In the last 2 weeks, have you been tired because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

6. In the last 2 weeks, my cough has made me feel anxious

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

9. In the last 2 weeks, exposure to paints or fumes has made me cough

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

10. In the last 2 weeks, has your cough disturbed your sleep?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

11. In the last 2 weeks, how many times a day have you had coughing bouts?

1	2	3	4	5	6	7
All of the time (continuously)	Most times during the day	Several times during the day	Some times during the day	Occasionally through the day	Rarely	None

12. In the last 2 weeks, my cough has made me feel frustrated

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

13. In the last 2 weeks, my cough has made me feel fed up

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

15. In the last 2 weeks, have you had a lot of energy?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

16. In the last 2 weeks, have you worried that your cough may indicate serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Some times when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

17.7 SF-12® Health Survey (SF-12)

SF-12v2™ Health Survey

(SF-12 v2 Standard, US Version 2.0)

To be completed by the PATIENT

Identification Number

Event

Directions: *This survey asks for your views about your health. This information will help you keep track of how you feel and how well you are able to do your usual activities. If you need to change an answer, completely erase the incorrect mark and fill in the correct circle. If you are unsure about how to answer a question, please give the best answer you can.*

Today's Date (MM/DD/YY)

/ /

Shade circles like this: ● Not like this: ⊗ ✓

Mark only one answer for each question. Please do not mark outside the circles or make stray marks on the questionnaire.

	Excellent	Very Good	Good	Fair	Poor
01. In general, would you say your health is:	○	○	○	○	○
The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
02. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○		
03. Climbing several flights of stairs	○	○	○		
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
04. Accomplished less than you would like	○	○	○	○	○
05. Were limited in the kind of work or other activities	○	○	○	○	○
During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
06. Accomplished less than you would like	○	○	○	○	○
07. Did work or activities less carefully than usual	○	○	○	○	○
08. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all ○	A little bit ○	Moderately ○	Quite a bit ○	Extremely ○
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...	All of the time	Most of the time	Some of the time	A little of the time	None of the time
09. Have you felt calm and peaceful	○	○	○	○	○
10. Did you have a lot of energy	○	○	○	○	○
11. Have you felt downhearted and depressed	○	○	○	○	○
12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	○	○	○	○	○

56129

15

-1 of 1-

17.8 Serious Adverse Events Anticipated in the Trial Population

The following is a list of SAEs by organ system that the Sponsor considers to be associated with the disease state being studied. Please note some of the listed events may need to present with severe intensity to meet the seriousness criteria (e.g., nausea and vomiting). The list does NOT change the reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in Section 9.5.5.1.1.2 (Serious Adverse Event Definition). The Investigator is required to follow the requirements detailed in Section 9.5.5.1.5 (Reporting and Documentation of Serious Adverse Events).

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicates they occur more frequently with trial drug compared with placebo, an expedited IND safety report may be submitted to the FDA.

Cardiovascular system:

- cardiac failure (including acute, chronic and congestive)
- ventricular failure (including ejection fraction decreased)
- pericardial effusion
- pericarditis
- supraventricular tachyarrhythmia
- hypotension

Pulmonary system:

- pulmonary arterial hypertension
- pulmonary hypertension
- FVC decreased
- respiratory-related hospitalizations
- acute exacerbations

17.9 Orthostatic Hypotension Assessment Manual

Orthostatic Hypotension Assessment Manual

Safety Vital Signs (Supine and Orthostatic) Per Protocol

Information about the orthostatic hypotension assessment and its intended use:

1. This assessment is purposed to inform whether treatment with HZN-825 is associated with orthostatic hypotension. This assessment is part of the overall safety evaluation of the current protocol.
2. This data is being collected as part of the overall safety analysis for the current trial.

The supine and orthostatic vital signs, as outlined in the protocol along with safety assessments, will be performed using either a standard manual or automated blood pressure cuff. A single measurement will be captured at each of the timepoints as indicated in the protocol and reviewed accordingly. For this assessment, heart rate and systolic and diastolic blood pressure will be measured after 5 minutes in supine resting position followed by measurement after 1 minute and 3 minutes in the standing position.

Positive orthostatic hypotension test is defined as the combination of a reduction of systolic blood pressure by ≥ 20 mmHg or reduction of diastolic blood pressure by ≥10 mmHg, **and** the presence of one or more of the following associated clinical symptoms:

- lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, presyncope or syncope

If positive for orthostatic hypotension, as defined above (inclusive of clinical symptoms), the subject should be assisted to lie back down in the supine position and monitored for clinical resolution of symptoms.

Prior to beginning the procedure, patients should be instructed to report any symptoms experienced throughout the assessment without probing for specific types of adverse events. If any symptoms occur during the assessment in combination with the blood pressure reductions noted above, they are considered as part of the orthostatic hypotension event and will not be recorded separately as individual adverse events.

If above symptoms are reported by the patient throughout the assessment, without the blood pressure reductions noted above, then the symptoms will only be recorded separately as adverse events if they meet any of the criteria below, and orthostatic hypotension will not be recorded.

- The symptoms are severe and/or require medical interventions
- The symptoms triggered by the OH assessment maneuver and persist for a significantly longer duration beyond the OH assessment period

- The symptoms are assessed not due to the maneuver of OH assessment

Lying Supine and Standing Pulse and Blood Pressure Test (See diagram 1)

A. Lying Supine

1. Subject should lay supine for approximately 5 minutes (+/- 1 minute), while practicing quiet breathing.
2. At the end of approximately 5 minutes (+/- 1 minute), the heart rate and blood pressure will be measured.
3. Both assessments of heart rate and blood pressure (including systolic and diastolic) will be collected.

B. Subject stands upright - One Minute Assessment upon standing

1. The subject should change positions from supine to standing.
2. Blood pressure and heart rate will be measured after the subject has been standing for 1 minute.
3. Both assessments of heart rate and blood pressure will be collected.

C. Subject remains standing upright – Three-Minute Assessment after the subject has stood up

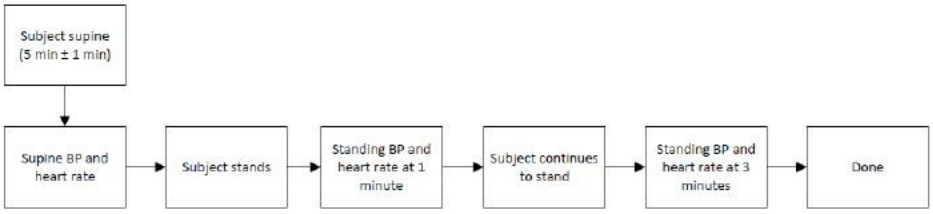
1. Blood pressure and heart rate will be measured after the subject has been standing for 3 minutes.
2. Both assessments of heart rate and blood pressure will be collected.

The symptoms i.e. lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, presyncope or syncope are reported by the patient throughout the OH assessment, without the blood pressure reductions (reduction in systolic BP ≥ 20 mmHg or diastolic BP ≥10mmHg), then these symptoms will be recorded as adverse events.
Please note that the above-mentioned reported symptoms during OH assessment should only be reported as adverse events separately if they meet any of the below criteria:

- The symptoms are severe and/or require medical interventions
- The symptoms were triggered by the OH assessment maneuver and persist for a significantly longer duration beyond the OH assessment period
- The symptoms are assessed not due to the maneuver of OH assessment

If these symptoms are reported in combination with the blood pressure reductions i.e. reduction in systolic BP ≥ 20 mmHg or diastolic BP ≥ 10 mmHg, these symptoms will be considered part of the orthostatic hypotension event and will not be reported separately.

Diagram 1 - Lying Supine and Standing Pulse and Blood Pressure Steps



Record all measurements on CRF

References

Johns Hopkins Medicine (2017 July). Guidelines for Assessing Orthostatic Hypotension Should Be Changed, New Study Recommends - 07/31/2017. Retrieved 28 Feb 2022 at www.hopkinsmedicine.org.

Centers for Disease Control and Prevention National Center for Injury Prevention and Control. Measuring_Orthostatic_Blood_Pressure-print.pdf (2017). Retrieved 28 Feb 2022 at www.cdc.gov.

Freeman R. (2018). Orthostatic Hypotension - State of Art JACC State of the Art Review. Journal of the American College of Cardiology. 72(11); 1295-1309.

17.10 Clinical SAE Report Form

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

SAE Report Form Completion Instruction

Complete the form by filling in the grey boxes electronically (by either double click and select 'checked' or double click and entering a text), printing out, signing and then fax or scan and email immediately and no later than 24 hours of awareness to:

Email (worldwide): svc-ags-in-us@amgen.com

Fax: +1-888-814-8653 (toll-free, within USA)

Fax: +44 (0)207-136-1046 (for non-USA)

If you must fax or email an SAE report form, you must also enter that event into the EDC system when it becomes available

Instructions are not provided for fields that are self-explanatory.
Suggestion: Save electronic form with Trial details for future use.

Enter all dates in the format DD-MMM-YYYY (e.g., 01-Jan-2020)

Date of this report	To be filled out by the investigator. Enter the date the form is being filled out
Protocol Number	Enter HZNP-HZN-825-303
Country	Country where the event occurred
Site Number	Enter number assigned to your site.
Subject Number	Enter the unique subject code or reference number specific for the trial.
Type of Report	Choose from the following: ***Initial Report*** - If this is the first notification of the serious adverse event (SAE)/adverse event of special interest (AESI). ***Follow up Report*** - If this is **not** the first notification of the SAE/AESI. A follow up report is necessary if there was information missing from initial report (e.g., stop date, outcome was ongoing, patient details, seriousness etc.), further information has been requested, there were errors to be corrected, or the initial report lacked a signature.
Age at Event Onset	Enter age in years at time of the event occurred.
Ethnicity	Tick appropriate box for ethnicity.
Race	Tick appropriate box for race.

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001 Page **1** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

Pregnant	If yes, enter the approximate week of pregnancy and also fill out the corresponding Clinical Trial Drug Exposure During Conception/ Pregnancy report form (**Formerly Horizon Legacy Form#: FOR-PHV-0002, Amgen # FORM- 510390**).
Is this event an adverse event of special interest (AESI)?	Check Yes or No (refer to protocol for details)
Date of first awareness of SAE/AESI by the site	Enter the date the first member of the investigator's trial team became aware of the SAE/AESI.
Reported event term	Enter the event term (a medical diagnosis whenever possible). The reporter may be the patient, caregiver, or health care provider, etc.
Start date of the adverse event	This is the date when the event started, which is not the date when the trial team was first aware or informed of the event. Enter (dd-mmm-yyyy)
Start time of the adverse event	Time when the adverse event started. (Enter time based on 24-hour clock i.e. 1300)
Date when the event became serious	This is the date when the event met one of the following seriousness criteria: **Results in Death** **Life threatening** **Requires inpatient or prolonged hospitalization** **Persistent or significant disability** **Congenital anomaly/birth defect** **Other medically important event (see seriousness criteria below)**
Stop date of the adverse event	Date the adverse event stopped. Enter (dd-mmm-yyyy)
Stop time of the adverse event	Time the adverse event stopped. (Enter time based on 24-hour clock i.e. 1300)
Seriousness Criteria	Tick as many of the criteria as apply. However, at least one of the criteria below must be ticked for an adverse event to qualify as **serious**. ***Results in Death*** *(death date: dd-mmm-yyyy)* ***Life-threatening*** *(places the subject at immediate risk of death from the reaction as it occurred, or it is suspected that the use or continued use of the product would result in the patient's death)* ***Persistent or significant disability/incapacity*** *(A substantial disruption of a person's ability to conduct normal life functions)* ***Requires inpatient or prolonged hospitalization*** *(Admission to the hospital for longer than 24 hours or prolongation of a hospital stay due to adverse event; admission and discharge dates: dd-mmm-yyyy)* ***Congenital anomaly/Birth defect***

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001 Page **2** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

	(Exposure to a medical product prior to conception or during pregnancy resulting in an adverse outcome in the child) ***Other medically important event**** **If important medical event is ticked, specify why it is considered medically important (particularly relevant if none of the others is ticked)*
Severity/Rheumatology Common Toxicity Criteria	This should not be confused with seriousness, which has a regulatory definition. See protocol for details. Rheumatology Common Toxicity Criteria: Grade 1 (mild) Grade 2 (moderate) Grade 3 (severe) Grade 4 (includes life-threatening)
Outcome	Choose from the following: ***Recovering/Resolving*** ***Recovered/Resolved*** ***Not Recovered/Not Resolved*** ***Recovered/Resolved with sequelae*** ***Fatal*** ***Unknown*** If the outcome is *"not recovered/not resolved", recovering/resolving"*, or *"unknown"* provide a follow up SAE/AESI report when the final outcome is available, or no further improvement is to be expected. If no further improvement is to be expected, enter the date of this information in the narrative section of the SAE/AESI form: e.g. as of dd-mmm-yyyy, event xxxxx is not going to resolve or improve.
Drug/Investigational Medicinal Product	Enter the information for all trial drugs that the subject was exposed to. If it is suspected that one of them caused the SAE/AESI, enter that one as Drug #1.
Relationship to HZN-825/Causality to Serious Adverse Event	List trial drugs in the same order as in the Drug/Investigational Medicinal Product grid. **For each drug, provide the investigator's assessment of causality.** **Choose from the following:** ***Yes, Related*** *- If the causal relationship between the trial drug and the SAE/AESI is at least a reasonable possibility.* ***No, Not Related*** *- If there is no causal relationship between the trial drug and the SAE/AESI i.e. the event is caused by something other than the trial drug (e.g. underlying disease, a concomitant medication, other trial*

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001 Page **3** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

	drug, etc.).
Action taken with Trial Drug	Select one of the options that is applicable to the **Action taken with HZN-825** as a result of the SAE/AESI ***Dose not Changed*** ***Dose Increased*** ***Dose Reduced*** ***Drug Interrupted*** ***Drug Withdrawn*** ***Not Applicable*** ***Unknown*** Action taken with trial drug to be considered **with regards to the adverse event**. Has any action been taken due to the adverse event (e.g. dose reduced or increased, trial drug temporarily interrupted, drug withdrawn etc.) Choose the option which is appropriate for the action that has been taken.
Relevant Concomitant Medication	List and describe relevant* details of concomitant medication (e.g. drug name (generic name [INN] preferred), start date and stop date (if applicable), dose and regimen, route and indication.) **Relevant to the event means either a medical or temporal influence is possible.*
Concomitant Procedure	Did the subject have any concomitant procedures performed for treatment purposes in relation to the SAE/AESI? Select Yes or No. If Yes, then document the date the procedure occurred, name of the procedure, and indication for why the procedure was performed.
Relevant Medical / Surgical History	Provide details of medical history conditions relevant* for assessment of the SAE/AESI (e.g. "hypertension"). Provide start date and stop date (if available) or tick the box ongoing, if the condition is persisting. Provide details of surgical history relevant for assessment of the SAE/AESI. **Relevant to the event means either a medical or temporal influence is possible.*

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001 Page **4** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

Diagnostic/Laboratory Tests Relevant to SAE/AESI(s)	Provide: Name of diagnostic/laboratory test Date of test (dd-mmm-yyyy) Result (including units as applicable) Normal reference range (as applicable)
Narrative Description of Serious Adverse Event/Adverse Event of Special Interest	Provide a narrative description of the event, similar in format to that of a discharge summary, but more concise and focused on the SAE/AESI. The description must have sufficient details for evaluation by the individuals reviewing the SAE/AESI. Include ***symptoms***, ***course*** and ***treatment of the adverse event***. Also summarize any relevant ***lab data*** or ***diagnostic tests***. *If applicable, include information if the route or frequency of trial drug administration has been changed but did not impact the dose.*
Reporter Information	The reporter is the person filling out the SAE form. A signature is required. If the reporter has the ability to sign electronically in a valid manner (compliant with 21 CFR 11 and/or Annex 11), he/she may apply an electronic signature. Every initial and follow-up report must be signed by the reporter prior to transmission to Sponsor.
Investigator Information	The investigator is the person who takes responsibility for the conduct of the trial at your site. If the investigator has the ability to sign electronically in a valid manner (compliant with 21 CFR 11 and/or Annex 11), he/she may apply an electronic signature. Note that submission of the report should not be delayed in order to get the investigator's signature. However, a signed report is required at the earliest opportunity.
Submission by email	The electronic file should be named appropriately and should include trial number (hyphens may be omitted if needed), the subject #, and version of the report. For example, the file name for an initial report in trial HZNP-HZN-825-303 for subject # 002-044 would be: HZNPHZN825303002044v1.doc The first follow-up report to that event would then be: HZNPHZN825303002044v2.doc The subject line of the email should read: SAE Report HZNP-HZN-825-303_Initial" or SAE Report HZNP-HZN-825-303_Follow-up #" Copy the trial medical monitor and your monitor on the email sent to Safety at: svc-ags-in-us@amgen.com

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001 Page **5** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

Submission by fax	The electronic file should be named appropriately and should include trial number (hyphens may be omitted if needed), the subject #, and version of the report. For example, the file name for an initial report in trial HZNP-HZN-825-303 for subject # 002-044 would be: HZNPHZN825303002044v1.doc The first follow-up report to that event would then be: HZNPHZN825303002044v2.doc The subject line of the fax should read "SAE Report HZNP-HPN-825-303_Initial" or "SAE Report HZNP-HZN-825-303_Follow-up #" Send a copy of the fax to the trial medical monitor and your monitor. US Fax: **+1-888-814-8653 (toll-free, within USA)** **Ex-US Fax: +44 (0)207-136-1046 (for non-USA)**
Follow-up reports	Follow-up reports are separate documents from initial reports. The Type of Report (Follow and #) must be completed. When creating a follow-up report, the header information (Protocol Number, Site Number, Subject Number, Medication or Randomization Number (if applicable) must be completed and be the same as used on the initial report. From there, ONLY fill in the boxes where you need to provide new, additional or corrected information. Line through any fields or boxes that are blank and provide reporter and investigator information and signatures as directed above. **Promptly, no later than 24 hours of awareness, submit the follow up as described via either fax or email.**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

Send completed Form by e-mail to (worldwide) to: svc-ags-in-us@amgen.com or by fax to: +1-888-814-8653 (toll-free, within USA) or +44 (0)207-136-1046 (for non-USA)

Date of Report (dd-mmm-yyyy):				
Protocol Number: HNZP-HZN-825-303	Country:	Site Number:	Subject Number:	Type of Report: ☐ Initial ☐ Follow-Up #

Age at Event Onset	Gender	Ethnicity	Race (Tick one box only)	Weight	Height	Pregnant (If yes, fill out pregnancy form)
	☐ Male ☐ Female	☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not specified	☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White/Caucasian ☐ Not specified ☐ Other	☐ Kg ☐ lbs	☐ cm ☐ inches	☐ No ☐ Yes, Week:

Is this a Serious Adverse Event (SAE)?	☐ Yes ☐ No
Is this an adverse event of special interest (AESI)?	☐ Yes ☐ No
Date of first awareness of SAE/AESI by site?	

Reported event term:	Start of adverse event: (e.g., 08-MAY-2021, 1300)	Date when adverse event became serious:	Stop of the adverse event: (e.g., 10-MAY-2021, 0600)
	Date: Time:		Date: Time:

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001

Page **7** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

Date of Report (dd-mmm-yyyy):				
Protocol Number: HNZP-HZN-825-303	**Country:**	**Site Number:**	**Subject Number:**	**Type of Report:** ☐ Initial ☐ Follow-Up #

Seriousness criteria: (Tick all that apply)	**Severity/ Rheumatology Common Toxicity Criteria:** (Tick the maximum severity applicable for the event)	**Outcome:** (Tick one box only)
☐ Results in Death Date of death: ☐ Life-threatening ☐ Persistent or significant disability / incapacity ☐ Requires inpatient or prolonged hospitalization Admission date: Discharge date: ☐ Congenital anomaly / Birth defect ☐ Other medically important event, please specify:	☐ Grade 1 – Mild ☐ Grade 2 – Moderate ☐ Grade 3 – Severe ☐ Grade 4 – Life-threatening	☐ Recovering / Resolving ☐ Recovered / Resolved ☐ Not recovered / Not resolved ☐ Recovered / Resolved with sequelae ☐ Fatal ☐ Unknown (an outcome of unknown is only expected if the subject is lost in follow-up)

Death Details
Cause of Death: Was an autopsy performed? Was a Death Certificate available?

Drug/Investigational Medicinal Product (IMP)
☐ **Not applicable, the subject did not receive IMP**

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001

Page **8** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

Date of Report (dd-mmm-yyyy):									
Protocol Number: HNZP-HZN-825-303		Country:		Site Number:		Subject Number:		Type of Report: ☐ Initial ☐ Follow-Up #	
Drug #	**Trial Drug/IMP** (Generic [INN]/Brand Name)	**Lot Number**	**Start Date** (DD-MMM-YYYY)	**Stop Date** (DD-MMM-YYYY)	**Dose**	**Regimen** (daily, weekly, monthly, etc.)	**Formulation** (e.g. tablet, solution, powder)	**Route of Administration**	**Indication**
1	HZN-825								

Drug #	**Trial Drug/IMP**	**Relationship to HZN-825/Causality to Serious Adverse Event/Adverse Event of Special Interest**	**Action taken with Trial Drug**
1		☐ Yes, Related ☐ No, Not related	☐ Dose not changed ☐ Dose reduced ☐ Dose increased ☐ Dose interrupted ☐ Drug withdrawn ☐ Unknown ☐ Not applicable

Relevant Concomitant Medication *(include any dietary supplements)*

Medication *Generic/(Brand Name)*	**Start Date** *(DD-MMM-YYYY)*	**Stop Date** *(DD-MMM-YYYY)*	**Dose**	**Regimen** *(daily, weekly, monthly, etc.)*	**Formulations/Route of Administration**	**Indication**

☐ *Tick the box if additional page(s) are attached*

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001

Page **9** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

Date of Report (dd-mmm-yyyy):									
Protocol Number: HNZP-HZN-825-303		Country:		Site Number:		Subject Number:		Type of Report: ☐ Initial ☐ Follow-Up #	
Drug #	**Trial Drug/IMP** (Generic [INN]/Brand Name)	**Lot Number**	**Start Date** (DD-MMM-YYYY)	**Stop Date** (DD-MMM-YYYY)	**Dose**	**Regimen** (daily, weekly, monthly, etc.)	**Formulation** (e.g. tablet, solution, powder)	**Route of Administration**	**Indication**
1	HZN-825								

Drug #	**Trial Drug/IMP**	**Relationship to HZN-825/Causality to Serious Adverse Event/Adverse Event of Special Interest**	**Action taken with Trial Drug**
1		☐ Yes, Related ☐ No, Not related	☐ Dose not changed ☐ Dose reduced ☐ Dose increased ☐ Dose interrupted ☐ Drug withdrawn ☐ Unknown ☐ Not applicable

Relevant Concomitant Medication *(include any dietary supplements)*

Medication *Generic/(Brand Name)*	**Start Date** *(DD-MMM-YYYY)*	**Stop Date** *(DD-MMM-YYYY)*	**Dose**	**Regimen** *(daily, weekly, monthly, etc.)*	**Formulations/Route of Administration**	**Indication**

☐ *Tick the box if additional page(s) are attached*

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001

Page **9** of **11**

Clinical SAE Report Form for HZNP-HZN-825-303
Version Date: 25 April 2024

Date of Report (dd-mmm-yyyy):				
Protocol Number: HNZP-HZN-825-303	**Country:**	**Site Number:**	**Subject Number:**	**Type of Report:** ☐ Initial ☐ Follow-Up #

Narrative Description of Adverse Event(s)
(Include symptoms, course, laboratory data, diagnostic tests, and treatment of the adverse event. If applicable, include information if the route or frequency of trial drug administration has been changed, but did not impact the dose)

☐ *Tick the box if additional page(s) are attached*

Reporter Information	Investigator Information
Printed Name:	Printed Name:
Title:	Title:
Date:	Date:
Telephone Number:	Telephone Number:
Fax Number:	Fax Number:
Country:	Country:
Email:	Email:
Signature: _____	Signature: _____
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to the Sponsor by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.	*I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to the Sponsor by the Investigator for this study, or by a Qualified Medical Person authorized by the Investigator for this study.*

FORM-510389, Effective Date: 25 Apr 2024, Version:1.0

Legacy # FOR-PHV-0001

Page **11** of **11**

17.11 Clinical Trial Drug Exposure During Conception/Pregnancy Form

AMGEN Form		
TITLE Clinical Trial Drug Exposure During Conception/Pregnancy	DOCUMENT NO FORM-510390	VERSION 1.0
	EFFECTIVE DATE 25 Apr 2024	PAGE Page **1** of **4**

For healthcare professional use only

Subject ID/Number:	**Protocol Number:**	**Country:**

Data Concerning Mother and Father / Family History

Parents	Trial Participant/Patient	Age (years)
Mother	☐ Yes, subject number: ☐ No	
Father	☐ Yes, subject number: ☐ No	

Hereditary diseases, malformations, chronic disease of expectant parents and in their families: ☐ Yes (if yes, please specify): ☐ No ☐ Unknown

Previous Pregnancies

Number of previous pregnancies:

Number of healthy children (no birth defects):

Number of children with birth defect: If any with birth defect please list (use 1 line per child):

Sex (m/f)	Birth Defects

Number of induced abortions:

Number of spontaneous abortions:

Number of stillbirths:

Current Pregnancy

Pregnancy is already terminated: ☐ Yes ☐ No* ☐ Unknown

*Week of gestation at the time of reporting:

First day of last menstruation:

Expected due date:

Period regular: ☐ Yes ☐ No ☐ Unknown

Drugs Used by the Trial Participant or Patient (Mother or Father)

Drug/IMP	Daily Dose (unit)	Indication	Therapy Date (from-to) dd-mmm-yyyy	

Drugs Used by the Mother During Pregnancy

Page **1** of **4**
Legacy # FOR-PHV-0002

AMGEN Form		
TITLE Clinical Trial Drug Exposure During Conception/Pregnancy	DOCUMENT NO FORM-510390	VERSION 1.0
	EFFECTIVE DATE 25 Apr 2024	PAGE Page **2** of **4**

Subject ID/Number:		Protocol Number:		Country:	
Trade Name/INN	**Daily Dose (unit)**	**Mode of Application**	**Indication**	**Therapy Date (from-to)** dd-mmm-yyyy	

☐ Please tick if additional page is attached

Course of Pregnancy

Prenatal Examinations	Date	Normal	Abnormal	If abnormal, please specify
Amniocentesis		☐	☐	
Testing of alpha-foetoproteins		☐	☐	
Chorionic villus sampling (CVS)		☐	☐	
Genetic Screening		☐	☐	
Ultrasound (US):		☐	☐	
1st US (9th to 12th week of gest.)		☐	☐	
2nd US (19th to 23rd week of gest.)		☐	☐	
3rd US (28th to 32nd week of gest.)		☐	☐	

Regular preventive medical checkups:	☐ Yes ☐ No ☐ Unknown
Potential Risks (drug, smoking, alcohol, x-ray examinations, etc.) and complications (e.g., hospitalization, infections during pregnancy, etc.)	☐ Yes (if yes, please specify): ☐ No ☐ Unknown

Data Concerning Childbirth and Child

Outcome of Pregnancy:
Date of Birth / Abortion / Stillbirth: or ☐ Unknown

Gestation Week	Vaginal Birth	Caesarian	Ventouse/Vacuum Extractor	pH of cord blood

AMGEN Form		
TITLE Clinical Trial Drug Exposure During Conception/Pregnancy	DOCUMENT NO FORM-510390 EFFECTIVE DATE 25 Apr 2024	VERSION 1.0 PAGE Page **3** of **4**

Subject ID/Number:		Protocol Number:		Country:
	☐	☐	☐	

Child	Sex	APGAR Score			Circumference of the Head	Birth Weight and Height		Fetal Lie	Outcome*	Abnormality	
	m/f	1	5	10	cm	Kg	Cm			Yes	No
1										☐	☐
2										☐	☐
3										☐	☐

*Outcome:
1. Live-birth
2. Spontaneous abortion (up to 20th week)
3. Stillbirth (20th – 27th week)
4. Stillbirth (from 28th week)
5. Induced abortion
6. Death of mother and child
7. Ectopic pregnancy, e.g. tubal pregnancy

Were there any complications during childbirth?	☐ Yes, please specify: ☐ No ☐ Unknown, please specify:
Does the child have any birth defect? *(Please also specify in cases of induced or spontaneous abortion, stillbirth, or death of neonate)*	☐ Yes, please specify: ☐ No ☐ Unknown, please specify:

Treating Gynecologist / Obstetrician*

*Please only complete if known and if consent is provided to contact the Gynecologist/Obstetrician

Identical with reporting physician: ☐ Yes ☐ No ☐ Unknown

Name: Street:

Postal Code/City: Telephone:

Pediatrician*

*Please only complete if known and if consent is provided to contact the Pediatrician

Pediatrician unknown: ☐ Yes ☐ No

Name: Street:

Postal Code/City: Telephone:

Comment / Assessment

If pregnancy was terminated early, or if any complications occurred during childbirth or with the neonate

Page **3** of **4**
Legacy # FOR-PHV-0002

AMGEN Form		
TITLE Clinical Trial Drug Exposure During Conception/Pregnancy	DOCUMENT NO FORM-510390	VERSION 1.0
	EFFECTIVE DATE 25 Apr 2024	PAGE Page **4** of **4**

Subject ID/Number:	**Protocol Number:**	**Country:**

In your view, is there reasonable evidence that these events are to be attributed to the drug exposure during pregnancy?

☐ Yes
☐ No
☐ Not Assessable, please explain (please add diagnostic findings if applicable):

Further comments:

☐ Please tick if additional page is attached

Investigator or Reporter

Printed Name:

Title:

Country:

Email:

Phone:

Fax:

Specialization:

Investigator or Reporter Signature: _____ **Date:**

Please return the completed form immediately and no later than 24 hours of awareness and submit via
Email (worldwide) to: svc-ags-in-us@amgen.com
or
Fax to: +1-888-814-8653 (toll-free, within USA) or to: +44 (0)207-136-1046 (for non-USA)

17.12 Lactation Notification Form

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: HZNP-HZN-825-303/20230132

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Confidential General and Administrative

Approval Signatures

Document Name: Protocol Amendment fipaxalparant 20230132 4

Document Description:

Document Number: CLIN-000353549

Approval Date: 11 Oct 2024

Type of Study Protocol: Amendment

Protocol Amendment No.: 4

Document Approvals	
Reason for Signing: Management	Name: [redacted] Date of Signature: 11-Oct-2024 17:02:39 GMT+0000

SUMMARY OF CHANGES
Protocol HZNP-HZN-825-303
Version 4.0 Amendment 3, incorporating Protocol Version 3.0

Key additions, revisions and clarifications to Version 3.0 of the protocol include:

- Updating the Sponsor's address.
- Revising the geographical regions and approximate number of sites in which the trial will be conducted.
- Making this a 2-part study by adding an optional, 52-week open-label extension to the trial (i.e., the Extension Phase [Part 2]). The Core Phase (Part 1) refers to the randomized, double-blind, placebo-controlled part of the trial.
- Clarifying the secondary objective pertaining to safety.
- Removing evaluation of metabolite(s) of HZN-825 in the 9th secondary objective, as this was deemed not necessary by communication with the United States Food and Drug Administration.
- Modifying one of the stratification factors to be *concomitant* use of approved IPF therapy rather than *prior* use and revising statistical analysis accordingly.
- Removing baseline FVC % predicted from statistical models due to the high collinearity with one of the stratification factors in the model.
- Specifying that the first secondary efficacy endpoint is the key secondary efficacy endpoint.
- Updating the p-values in the description of the tipping point analysis.
- Specifying that there will be an interim analysis [redacted]
- Deleting mention of adjustment to account for the futility analysis. Since there will be a futility analysis during the interim analysis, with no intention to stop the trial due to efficacy evaluation, there is no need to adjust the significant value for multiple comparisons at interim analysis.
- Updating p-values due to updated overall significance level (alpha = 0.10, 2-sided).
- Changing the testing procedure for multiple comparisons from a Hochberg testing procedure to a hierarchical testing procedure.
- Specifying that p-values for other secondary endpoints will not be used for inferential purposes.
- Updating description of the sample size estimate; the target enrollment was reduced to 135 subjects from 360 subjects.
- Modifying inclusion criteria with respect to age, current and initial diagnosis of idiopathic pulmonary fibrosis (IPF), current IPF therapy and diffusing capacity of the lungs for carbon monoxide (DLCO); clarifying inclusion criteria pertaining to lung

high-resolution computed tomography (HRCT) and removing mention of honeycombing; clarifying that vaccination status is to be determined according to the Investigator's discretion; and removing examples of vaccines.

- Including further guidance about acceptable use of restricted medications as part of the entry criteria evaluation in exclusion criterion 5.
- Clarifying that subjects who complete the Double-blind Treatment Period in the Core Phase may be eligible for the Extension Phase.
- Changing the primary analysis set from the intent-to-treat analysis set to the full analysis set.
- Adding new requirements around condom use, aligning text with Section 9.5.5.2 in exclusion criterion 8 and adding clarification around abstinence as a contraceptive method.
- Specifying restrictions in exclusion criterion 8 regarding egg/ova donation and sperm donation.
- Making human immunodeficiency virus (HIV) testing optional (with subject consent) at Visit 1.
- Modifying the exclusion criteria pertaining to total bilirubin and confirmed grade of laboratory abnormality.
- Removing the exception of previous HZN-825 exposure from an exclusion criterion.
- Clarifying the definition of active hepatitis B and reformatting exclusion criterion 13 for clarity.
- Allowing subject visits at Weeks 22, 34 and 46 to be performed at locations other than the trial site.
- Indicating that histopathology is not required to determine subject eligibility.
- Adding detail around the baseline lung HRCT.
- Adding a citation (Raghu et al., 2022) pertaining to updates to the consensus for the diagnosis of IPF.
- Updating the protocol with information from the current Investigator's Brochure (Version 8) and a Phase 1 drug-drug interaction trial with respect to clinical experience with HZN-825.
- Including a section on the benefit/risk assessment for HZN-825.
- Clarifying that the adjudication committee will only pertain to the Core Phase.
- Providing description regarding Horizon unblinded personnel involvement in decisions on future dose selection and future trial design during the interim analysis.
- Specifying that a clinically significant laboratory or electrocardiogram (ECG) abnormality may lead to removal of subjects from treatment.
- Including restricted medication use as a specific reason for discontinuation from trial treatment.

- Specifying that attempts should be made to contact subjects who are initially lost to follow-up.
- Adding a section on changes to background therapy for IPF.
- Adding rationale to support the safety of up to a 600 mg dose of HZN-825.
- Specifying that any completely missed dose should be recorded on the electronic case report form (eCRF).
- Updating restrictions regarding concomitant medications and removing P-glycoprotein (P-gp) inhibitors from the list of restricted medications because the strong P-gp transporter inhibitor itraconazole had no impact on HZN-825 exposure at clinically relevant doses in a Phase 1 trial.
- Deleting the table that delineated specific rescue therapy, as such therapy will be determined in consultation with the trial Medical Monitor.
- Including some additional cautions around use of specific concomitant medications and information regarding concomitant therapy.
- Stressing the importance of compliance with trial drug.
- Adding a reference to American Thoracic Society (ATS) guidelines for the 6-minute walk test (6MWT).
- Clarifying language for obtaining DLCO measurement.
- Deleting mention of collection of data on paper, as all data will be collected electronically for the trial.
- Clarifying that subject exit interviews will be covered by a separate protocol.
- Providing detail regarding taking trial drug with a meal.
- Adding the definition of a suspected adverse reaction.
- Clarifying when pre-existing conditions should be reported as AEs.
- Aligning language throughout the protocol with that in the updated Orthostatic Hypotension Assessment Manual.
- Clarifying documentation and reporting for medication errors.
- Specifying that a repeat resting ECG should be conducted if a clinically significant ECG result is obtained.
- Specifying the urinalysis parameters.
- Including the estimated amount of total blood volume that will be collected from each subject.
- Alerting trial personnel that the actual assessment instruments used may differ from those in Section 17 of the protocol.
- Changing the Medical Monitor.
- Updating the SF-12® Health Survey to the most current version.

- Updating the Orthostatic Hypotension Assessment Manual and protocol language to align the process of assessing orthostatic hypotension with current guidelines, to clarify the manual to make the process more understandable and improve the method of data collection for orthostatic hypotension.

Changes considered not key, minor wording changes and correction of minor typographical errors are not detailed below.

SUMMARY TABLE OF CHANGES
Protocol Version 3.0 (11 October 2021) to Protocol Version 4.0, Amendment 3 (01 December 2022)

Text Version 3.0, Amendment 2 11 October 2021	Amended Text Version 4.0, Amendment 3 01 December 2022	Reason for Change
First Page and Title Page **Horizon Therapeutics Ireland DAC** **Connaught House, 1st Floor** **1 Burlington Road** **Dublin D04 C5Y6** **Ireland**	**First Page and Title Page** **Horizon Therapeutics Ireland DAC** **70 St. Stephen's Green** **Dublin 2** **D02 E2X4** **Ireland**	*To update the Sponsor's address*
Synopsis – Number and Country of Trial Sites, Section 6 Investigators and Trial Administrative Structure and Section 9.1 Overall Trial Design and Plan Approximately 100 sites in the United States, Europe, Asia, Australia and New Zealand	**Synopsis – Number and Geographical Regions of Trial Sites, Section 6 Investigators and Trial Administrative Structure and Section 9.1 Overall Trial Design and Plan** Approximately 85 sites in North America, Europe, South America, Africa, Asia (including Japan) and Australia.	*To revise the geographical regions and approximate number of sites in which the trial will be conducted*
Synopsis – Objectives Not applicable; text added to v4.0 of the protocol.	**Synopsis – Objectives and Section 8** 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).	*To add an optional OLE to the trial*
Synopsis – Secondary Objectives and Section 8.2 Secondary Objectives 8. Assess safety and tolerability of HZN-825 based on adverse events (AEs), serious adverse events (SAEs) and adverse event of special interest (AESI).	**Synopsis – Secondary Objectives and Section 8.1.2 Secondary Objectives** 8. Assess safety and tolerability of HZN-825, inclusive of, but not limited to, adverse events (AEs), SAEs and AESI.	*To clarify the secondary objective pertaining to safety*

Synopsis – Secondary Objectives and Section 8.2 Secondary Objectives 9. Evaluate the pharmacokinetics (PK) of HZN-825 and metabolite(s).	**Synopsis – Secondary Objectives and Section 8.1.2 Secondary Objectives** 9. Evaluate the pharmacokinetics (PK) of HZN-825.	*To remove evaluation of metabolite(s) of HZN-825*
Synopsis – Criteria for Evaluation and Pharmacokinetic Endpoint, Section 9.5.2 Pharmacokinetic Measurements, Section 9.6.1.5 Pharmacokinetic Endpoint and Section 9.6.7 Pharmacokinetic Analyses The phrase: "HZN-825 and metabolite(s)"	**Synopsis – Criteria for Evaluation and Pharmacokinetic Endpoint, Section 9.5.2 Pharmacokinetic Measurements, Section 9.6.1.1.6 Pharmacokinetic Endpoint and Section 9.6.1.7 Pharmacokinetic Analyses** This phrase was changed to: "HZN-825"	*To remove evaluation of metabolite(s) of HZN-825*
Synopsis – Objectives Not applicable; text added to v4.0 of the protocol.	**Synopsis – Objectives and Section 8.2 Part 2 (Extension Phase)** Objectives were added for Part 2 (Extension Phase); see **Part 2 (Extension Phase)** in the synopsis and Section 8.2.	*To add an optional OLE to the trial*
Synopsis – Trial Design This 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. Subjects will be screened within 8 weeks prior to the Baseline (Day 1) Visit. Approximately 360 subjects who meet the trial eligibility criteria will be randomly assigned 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. Prior use of approved IPF therapy (i.e., nintedanib or pirfenidone): yes or no 2. FVC % predicted at Baseline: ≥70% or <70% The trial 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 return to the clinic for trial visits at Week 4 and every 6 weeks thereafter until Week 52.	**Synopsis – Trial Design** HZNP-HZN-825-303 (HARBOR) 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. The trial will include up to an 8-week Screening Period and a 52-week Double-blind Treatment Period in the Core Phase and 52 weeks of open-label HZN-825 treatment in the Extension Phase. During the Core Phase, subjects will be screened within 8 weeks prior to the Baseline (Day 1) Visit. Approximately 135 subjects who meet the trial eligibility criteria will be randomly assigned 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% During the Core Phase, 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.	*To add an optional OLE to the trial, reduce the targeted enrollment and modify one of the stratification factors as concomitant use of approved IPF therapy is now allowed*

Synopsis – Trial Design, Section 9.1 Overall Trial Design and Plan A futility analysis will be performed when [redacted]	**Synopsis – Trial Design, Section 9.1 Overall Trial Design and Plan** An interim analysis with a futility analysis will be performed when [redacted]	*To specify that there will be an interim analysis at Week 28*
Synopsis – Trial Design 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 that may involve subject safety or dose selection; otherwise, unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management. The IDMC will also review accumulating safety data to ensure subject safety.	**Synopsis – Trial Design** 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. A Horizon unblinded team may also aid in dose selection and future trial design.	*To mention that Horizon unblinded personnel not involved directly in trial conduct may be involved in decisions on dose selection*
Synopsis – Trial Design Not applicable; figure added to v4.0 of the protocol.	**Synopsis – Trial Design and Figure 9.1** A trial design figure for the Extension Phase was added; see **Extension Phase** figure and **Figure 9.2**.	*To add an optional OLE to the trial*
Synopsis – Subject Population Approximately 360 subjects between the ages of 18 and 80 years, inclusive, with IPF will be enrolled.	**Synopsis – Subject Population** Approximately 135 subjects ≥18 years of age with IPF will be enrolled.	*To reduce the targeted enrollment and modify the inclusion criteria with respect to age*
Synopsis – Inclusion Criteria and Section 9.3.1 Inclusion Criteria 2. Male or female between the ages of 18 and 80 years, inclusive, at Screening. 3. Current diagnosis of IPF, as defined by American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) guidelines [Raghu et al., 2018] and determined by	**Synopsis – Inclusion Criteria and Section 9.3.1 Inclusion Criteria** 2. Male or female ≥18 years of age at Screening. 3. Current diagnosis of IPF, as defined by ATS/ERS/JRS/ALAT guidelines [Raghu et al., 2022] and determined by central review; the date of initial diagnosis of IPF should be ≤7 years prior to Screening.	*To modify the inclusion criteria with respect to age, current and initial diagnosis of IPF, current IPF therapy and DLCO; to clarify*

central review; the date of initial diagnosis of IPF should be ≥1 year to ≤7 years prior to Screening. 4. Not currently being treated with specific IPF therapy for the reasons below: a. intolerant or not responsive to approved IPF therapies b. ineligible to receive approved IPF therapies c. declines approved IPF therapies 5. Lung HRCT historically performed within 6 months prior to the Screening Visit and according to the minimum requirements for IPF diagnosis by central review based on subject's HRCT. If an evaluable HRCT is not available within 6 months prior to Screening, an HRCT will be performed at Screening to determine eligibility, according to the same requirements as the historical HRCT. 6. HRCT shows ≥10% to <50% parenchymal fibrosis (reticulation) and <25% honeycombing and the extent of fibrotic changes is greater than the extent of emphysema on the most recent HRCT scan (central reviewer determined). 7. Meets all of the following criteria during the Screening Period: a. FVC ≥45% and ≤80% predicted of normal b. forced expiratory volume in 1 second (FEV_1)/FVC ≥0.7 c. DLCO corrected for hemoglobin is ≥30% and ≤90% predicted of normal 9. Vaccinations are up to date given age, comorbidities (e.g., severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), pneumococcal pneumonia, herpes zoster, tetanus) and local availability prior to trial drug dosing.	4. No recent changes or planned changes to the dose or regimen for IPF therapy, defined as: • Receiving a stable dose of IPF-approved therapy (i.e., nintedanib or pirfenidone) for a minimum of 3 months prior to Day 1 with no plans to change the background regimen during trial participation, or • Not currently receiving background IPF-approved therapy at Screening (either naïve to IPF-approved therapy or previously discontinued any IPF-approved therapy at least 4 weeks prior to Day 1 or drug-specific, 5 half-lives elimination period if longer than 4 weeks), and with no current plans to restart treatment during trial participation • Subjects receiving any additional agent for IPF therapy must be on a stable regimen for at least 3 months prior to Day 1 with no current plans to change the treatment regimen during trial participation. Any previously discontinued therapy used to treat IPF must have been discontinued at least 4 weeks prior to Day 1 or 5 half-lives for that specific therapy must have elapsed, whichever is longer, with no plans to restart the therapy during trial participation. 5. Lung HRCT historically performed within 6 months prior to the Screening Visit and according to the minimum requirements for IPF diagnosis by central review based on subject's HRCT. If an evaluable HRCT is not available within 6 months prior to Screening, an HRCT will be performed at Screening to determine eligibility, according to the same requirements as the historical HRCT. The HRCT must demonstrate an usual interstitial pneumonia or probable usual interstitial pneumonia pattern based on central review vendor interpretation. Histopathology in combination with HRCT results supportive of an IPF or IPF likely diagnosis according to Raghu et al., 2022 can be submitted to support subject eligibility. 6. HRCT shows ≥10% to <50% parenchymal fibrosis (reticulation) and the extent of fibrotic changes is greater than	*inclusion criteria pertaining to lung HRCT and remove mention of honeycombing; clarify that vaccination status is to be determined according to the Investigator's discretion and remove examples of vaccines*

	the extent of emphysema on the most recent HRCT scan (central reviewer determined). 7. Meets all of the following criteria during the Screening Period, as determined by central review: a. FVC ≥45% predicted of normal b. forced expiratory volume in 1 second (FEV_1)/FVC ≥0.7 c. DLCO corrected for hemoglobin is ≥25% and ≤90% predicted of normal 9. Vaccinations are up to date, according to the Investigator's discretion, given age, comorbidities and local availability prior to trial drug dosing.	
Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria 5. Use of any of the following therapies within 4 weeks prior to Screening, during the Screening Period or planned during the trial: prednisone at steady dose >10 mg/day or equivalent or cyclosporine A. Prednisone ≤10 mg/day (or equivalent dosing of glucocorticoids) is allowed. Treatment with any other immunosuppressant during the Screening Period through the end of trial participation will require consultation with and approval by the trial Medical Monitor. See Table 9.1 and Table 9.2 for full details. 8. Women of childbearing potential (WOCBP) or male subjects not agreeing to use highly effective method(s) of birth control throughout the trial and for 1 month after last dose of trial drug. Male subjects must refrain from sperm donation and females from egg/ova donation for this same time period. Women are considered of childbearing potential if they are not postmenopausal and not surgically sterile (documented bilateral salpingectomy, bilateral oophorectomy or hysterectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea,	**Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria** 5. Use of any of the following therapies within 4 weeks prior to Screening, during the Screening Period or planned during the trial: prednisone at steady dose >10 mg/day or equivalent or cyclosporine. Change in regimen or dosage of any immunosuppressant during the Screening Period through the end of trial participation will require consultation with and approval by the trial Medical Monitor. See Section 9.4.9 for full details. Avoiding the use of listed prohibited treatments must not be considered detrimental and must be indicated by the treating physician. Subjects must not be withdrawn from any standard-of-care treatment that is considered necessary for the clinical management of the subject in order to fulfill the trial eligibility requirements. 8. Women of childbearing potential (WOCBP) or male subjects not agreeing to use highly effective method(s) of birth control throughout the trial and for 4 weeks after last dose of trial drug. Females must refrain from egg/ova donation for 4 weeks after the last dose of trial drug and males must refrain from sperm donation for 3 months after the last dose of trial drug. Women are considered of childbearing potential if they are not postmenopausal and not surgically sterile (documented bilateral salpingectomy, bilateral oophorectomy or hysterectomy). A postmenopausal state is defined as no menses for 12 months	*To change restrictions regarding concomitant medications and add language to clarify that avoiding the use of the prohibited medications must not be detrimental and the subjects must not be deprived of the standard of care if deemed necessary for the clinical management of the subject, include requirement for condom use and for consistency with language in*

a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. 9. Pregnant or lactating women and women who plan to become pregnant or breast feed during the trial and within 1 month after the last dose of trial drug. 12. Known history of positive test for human immunodeficiency virus. 13. Active hepatitis (hepatitis B: positive hepatitis B surface antigen and positive anti-hepatitis B core antibody [anti-HBcAb] and negative hepatitis B surface antibody [HBsAb] or positive for HBcAb with a positive test for HBsAb and with presence of hepatitis B virus DNA at Screening; hepatitis C: positive anti-hepatitis C virus [anti-HCV] and positive RNA HCV). 19. Total bilirubin >2 × ULN. Subjects with documented diagnosis of Gilbert's syndrome may be enrolled if their total bilirubin is ≤3.0 mg/dL. 21. Any verified Grade 4 laboratory abnormality. 23. Exposure to an experimental drug (with the exception of HZN-825) or experimental vaccine within either 30 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is the longest, prior to Day 1.	without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Fertile male subjects must use a condom throughout the trial and for 4 weeks after the last dose of trial drug. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. 9. Pregnant or lactating women and women who plan to become pregnant or breast feed during the trial and within 4 weeks after the last dose of trial drug. 12. Known history of positive test for human immunodeficiency virus (HIV). 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. 13. Active hepatitis (any of the following at Screening): *Hepatitis B*: • positive hepatitis B surface antigen • positive for anti-hepatitis B core antibody (anti-HBcAb) and a positive test for hepatitis B surface antibody (HBsAb) and presence of hepatitis B virus DNA • positive for HBcAb and a negative test for HBsAb and presence of hepatitis B virus DNA *Hepatitis C*: • positive anti-hepatitis C virus (anti-HCV) and positive HCV RNA. 19. Total bilirubin >1.5 × ULN. Subjects with documented diagnosis of Gilbert's syndrome may be enrolled if their total bilirubin is ≤3.0 mg/dL. 21. Any confirmed Grade 3 or higher laboratory abnormality. 23. Exposure to an experimental drug or experimental vaccine within either 30 days, 5 half-lives of the test agent, or twice the	*Section 9.5.5.2, specify restrictions regarding egg/ova and sperm donation, make HIV testing optional (with subject consent), clarify the definition of active hepatitis B and reformat for clarity, modify exclusion criterion pertaining to total bilirubin and confirmed grade of laboratory abnormality and remove the exception of previous HZN-825 exposure from criterion 23*

	duration of the biological effect of the test agent, whichever is the longest, prior to Day 1.	
Synopsis Not applicable; text added to v4.0 of the protocol.	**Synopsis and Section 9.3.2 Eligibility Criteria for the Extension Phase** Eligibility criteria were added for the Extension Phase; see **Eligibility Criteria for the Extension Phase** in the synopsis and **Section 9.3.2**.	*To add an optional OLE to the trial*
Synopsis – Dose Regimen/Route of Administration Not applicable; text added to v4.0 of the protocol.	**Synopsis – Dose Regimen/Route of Administration** Extension Phase: The dose regimen for all subjects will be HZN-825 300 mg BID. Subjects will take 2 HZN-825 150 mg tablets orally in the morning and evening with a meal. The dose for the Extension Phase may be modified based on the results of the Core Phase.	*To add an optional OLE to the trial*
Synopsis – Duration of Treatment and Follow-up and Schematic of Trial Design The planned duration of the Double-blind Treatment Period is 52 weeks. All subjects who complete the Double-blind Treatment Period will be eligible to enter into a 52-week open-label extension trial (HZNP-HZN-825-304). Subjects not entering the open-label extension trial will return to the clinic 4 weeks after the last dose of trial drug for a Safety Follow-up Visit.	**Synopsis – Duration of Treatment and Follow-up and Schematic of Trial Design (Core Phase)** The planned duration of the Double-blind Treatment Period of the Core Phase is 52 weeks. All subjects who complete the Double-blind Treatment Period may be eligible to enter into the Extension Phase of the trial and receive 52 weeks of open-label HZN-825. The total maximum exposure to trial drug during the trial is 104 weeks. Subjects not entering the Extension Phase of the trial will return to the clinic 4 weeks after the last dose of trial drug for a Safety Follow-up Visit.	*To clarify that subjects who complete the Double-blind Treatment Period may be eligible for the Extension Phase of the trial*
Synopsis – Statistical Analyses Secondary Efficacy Endpoints 1. Proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52.	**Synopsis – Statistical Analyses** Key Secondary Efficacy Endpoint Proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52.	*To specify a key secondary efficacy endpoint*

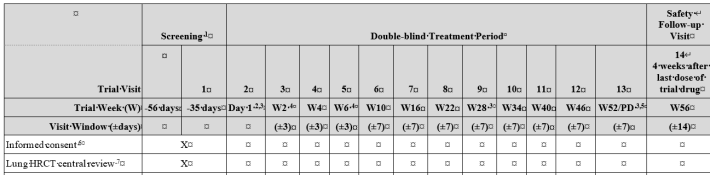
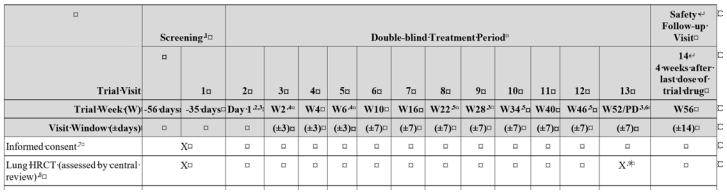
Synopsis – Statistical Analyses Statistical Analysis of Efficacy and Safety Endpoints Efficacy analyses will be performed on the intent-to-treat (ITT) analysis set, consisting of all subjects who are randomized to treatment; subjects will be analyzed according to the treatment group to which they were randomized. Safety analyses will be performed on the safety analysis set, consisting of all subjects who receive at least 1 dose or partial dose of trial drug. Efficacy The estimand for the primary efficacy analyses will be constructed to compare the primary endpoint between each dose regimen of HZN-825 and placebo using the treatment policy strategy approach to intercurrent events. All subjects who are randomized will be included in the primary efficacy analyses (ITT analysis set).	**Synopsis – Statistical Analyses** Statistical Analysis of Efficacy and Safety Endpoints Efficacy analyses will be performed on the full analysis set (FAS), consisting of all subjects who are randomized to treatment and take at least 1 dose of trial drug; subjects will be analyzed according to the treatment group to which they were randomized. Safety analyses will be performed on the safety analysis set, consisting of all subjects who receive at least 1 dose or partial dose of trial drug. Efficacy The estimand for the primary efficacy analyses will be constructed to compare the primary endpoint between each dose regimen of HZN-825 and placebo using the treatment policy strategy approach to intercurrent events. All subjects who are randomized and take at least 1 dose of trial drug will be included in the primary efficacy analyses (FAS).	*To change the primary analysis set from the intent-to-treat analysis set to the full analysis set*
Synopsis – Statistical Analyses and Section 9.6.3 Primary Efficacy Endpoint Analysis A mixed model for repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the data using observed change in FVC % predicted values from all planned post-Baseline assessments (i.e., Weeks 4, 16, 28, 40 and 52) with covariates of Baseline FVC % predicted value, stratification factors (prior use of IPF therapy [yes, no] and FVC % predicted at Baseline [≥70%, <70%]), treatment group, visit and visit-by-treatment group interaction. The unstructured variance-covariance matrix will be used in the model. Treatment group least squares means, associated standard error (SE) and their differences (each HZN-825 group minus placebo separately), SE of the difference, 95% confidence intervals (CIs) and p-value overall and for each visit will be provided.	**Synopsis – Statistical Analyses and Section 9.6.1.3 Primary Efficacy Endpoint Analysis** A mixed model for repeated measures (MMRM) analysis of covariance (ANCOVA) model will be fit to the data using observed change in FVC % predicted values from all planned post-Baseline assessments (i.e., Weeks 4, 16, 28, 40 and 52) with covariates of stratification factors (concomitant use of IPF therapy [yes, no] and FVC % predicted at Baseline [≥70%, <70%]), treatment group, visit and visit-by-treatment group interaction. The unstructured variance-covariance matrix will be used in the model. Treatment group least squares means, associated standard error (SE) and their differences (each HZN-825 group minus placebo separately), SE of the difference, 90% confidence intervals (CIs) and p-value overall and for each visit will be provided.	*To modify statistical analysis as concomitant use of approved IPF therapy is now allowed and change the CI from 95% to 90% and remove baseline FVC % predicted from the model*

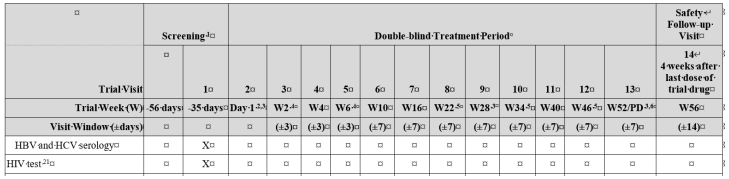
Synopsis – Statistical Analyses and 9.6.3 Primary Efficacy Endpoint Analysis A tipping point analysis will estimate the difference in true values among unobserved data that must occur to change the conclusion for each dose (i.e., change the result for each dose from p≤0.025 to p>0.025).	**Synopsis – Statistical Analyses and 9.6.1.3 Primary Efficacy Endpoint Analysis** A tipping point analysis will estimate the difference in true values among unobserved data that must occur to change the conclusion for each dose (i.e., change the result for each dose from p≤0.10 to p>0.10).	*To update the p-values in the description of the tipping point analysis*
Synopsis – Statistical Analyses and 9.6.4 Secondary Efficacy Endpoint Analyses The logistic model will provide odds ratio, its 95% CI and p-value for comparing each HZN-825 group with the placebo group.	**Synopsis – Statistical Analyses and 9.6.1.4 Secondary Efficacy Endpoint Analyses** The logistic model will provide odds ratio, its 90% CI and p-value for comparing each HZN-825 group with the placebo group.	*To change the CI from 95% to 90%*
Synopsis – Statistical Analyses and Section 9.6.8 Interim Analyses After approximately [redacted] an analysis of the primary efficacy endpoint will be conducted using unblinded, comparative data. This analysis will have 2 potential outcomes: • If neither dose regimen of HZN-825 shows better efficacy compared to placebo with an acceptable safety profile, the trial will be discontinued for futility. • If 1 or both dose regimens of HZN-825 show better efficacy compared to placebo with an acceptable safety profile, the trial will continue with no changes. The futility analysis will not be used to make a positive determination of efficacy to stop the trial. Conditional power will be used to determine which of the options is chosen, with a conditional power of ≥10% required for at least 1 dose regimen to continue the trial.	**Synopsis – Statistical Analyses and 9.6.1.8 Interim Analysis** An interim analysis of the primary efficacy endpoint will be conducted [redacted] This analysis will have 2 potential outcomes: • If neither dose regimen of HZN-825 shows better efficacy compared to placebo with an acceptable safety profile, the trial will be discontinued for futility. • If 1 or both dose regimens of HZN-825 show better efficacy compared to placebo with an acceptable safety profile, the trial will continue with no changes. The futility analysis will not be used to make a positive determination of efficacy to stop the trial. Conditional power will be used to determine which of the options is chosen, with a conditional power of ≥10% required for at least 1 dose regimen to continue the trial. Other statistics, such as Bayesian statistics, may also be used for the futility analysis and dose selection.	*To specify that there will be an interim analysis at Week 28*

Synopsis – Statistical Analyses and Section 9.6.8 Interim Analyses Not applicable; text added to v4.0 of the protocol.	**Synopsis – Statistical Analyses and Section 9.6.1.8 Interim Analysis** To support the dose selection and as part of the Week 28 unblinded interim analysis, the FVC % predicted change from Baseline at Week 28 will be evaluated in subjects who were randomized with concomitant standard-of-care treatment at Baseline. Approximately 60 subjects in the standard-of-care stratum with 28 weeks of data (approximately 20 subjects per arm) will be included. The positive signal in the FVC % predicted change from Baseline at Week 28 and related results in standard-of-care subjects will support the dose selection and future trial design.	*To add statistical analysis for data from standard-of-care subjects to support dose selection at the interim analysis at Week 28*
Synopsis – Statistical Analyses, Section 9.1 Overall Trial Design and Plan, Section 9.4.8 Blinding and Unblinding and Section 9.6.8 Interim Analyses 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 studies. For additional details, please refer to the IDMC charter for this study.	**Synopsis – Statistical Analyses, Section 9.1 Overall Trial Design and Plan, Section 9.4.8 Blinding and Unblinding and Section 9.6.1.8 Interim Analysis** 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.	*To provide description regarding Horizon unblinded personnel involvement in decisions on future dose selection and future trial design at the interim analysis*

Synopsis – Statistical Analyses The overall statistical level is α=0.05 (2-sided). Because 2 dose regimens of HZN-825 will be compared to placebo, a Hochberg testing procedure will be used for multiple comparison [Hochberg, 1988]. An additional adjustment will be made to account for the futility analysis. Even though there is no chance to stop the trial at the futility analysis for conclusion of benefit, a small adjustment to the type I error rate (0.001, 2-sided) will be made to account for the unblinded, comparative summary. Therefore, we will use α=0.049 (2-sided) in the final analysis. The Hochberg testing procedure will be used for the primary endpoint first. If one or two dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur. If both HZN-825 are statistically significantly better than the placebo for primary efficacy endpoint, the Hochberg testing procedure will be used for the key secondary endpoint similar as the primary endpoint was performed. If both dose regimens of HZN-825 for the key secondary endpoint are considered significant, subsequent secondary endpoints will be tested sequentially within each dose regimen in the order as above, using α=0.0245 (2-sided) in a sequential testing procedure. Although p-values will be provided for exploratory endpoints, they will not be used for inferential purposes.	**Synopsis – Statistical Analyses** The overall statistical level is α=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, α=0.10 (2-sided) will be used in the final 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.	*Since there will be a futility analysis during the interim analysis with no intention to stop the trial due to efficacy evaluation, there is no need to adjust the significant value for multiple comparisons at interim analysis; to update the overall statistical level of the trial; to replace the Hochberg procedure with a hierarchical procedure and specify that p-values for other secondary endpoints will not be used for inferential purposes*

Synopsis – Statistical Analyses and Section 9.6.4 Secondary Efficacy Endpoint Analyses The key secondary endpoint will be the proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52 and will be analyzed using a logistic regression model with baseline FVC % predicted, treatment group and stratified by factors used for stratifying the randomization.	**Synopsis – Statistical Analyses and Section 9.6.1.4 Secondary Efficacy Endpoint Analyses** The key secondary endpoint will be the proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52 and will be analyzed using a logistic regression model with treatment group and stratified by factors used for stratifying the randomization.	*To remove baseline FVC % predicted from the model*
Synopsis – Sample Size Estimate and Section 9.6.10 Sample Size and Power Considerations A total of 360 subjects (120 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 4% and a common standard deviation is 9%, a sample size of 120 subjects per treatment group will provide 88% power to detect a clinically important difference between each posology of HZN-825 and placebo at a significance level of 0.0245, 2-sided.	**Synopsis – Sample Size Estimate and Section 9.6.3 Sample Size and Power Considerations** 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.	*To reduce target enrollment, update values for significance level due to updated overall significance level (alpha = 0.10, 2-sided) and update description of the sample size estimate*
Synopsis and Section 9.6 Statistical Methods and Determination of Sample Size No applicable; text added to v4.0 of the protocol.	**Synopsis and Section 9.6.2** Statistical analyses were added for the Extension Phase; see statistical analyses for the Extension Phase in the synopsis (**Extension Phase**) and Section 9.6.2.	*To add an optional OLE to the trial*

Section 2.1 Schedule of Assessments 	**Section 2.1 Schedule of Assessments During the Core Phase** 	*To combine rows in the Schedule of Assessments for the Core Phase pertaining to lung HRCT and allow subject visits at Weeks 22, 34 and 46 to be performed at locations other than the investigational site*
Section 2.1 Schedule of Assessments Not applicable; footnote added to v4.0 of the protocol.	**Section 2.1 Schedule of Assessments During the Core Phase** 5. Visits may be conducted as home health visits, as available within local regions.	*To allow visits at Weeks 22, 34 and 46 to be conducted at locations other than the investigational site*
Section 2.1 Schedule of Assessments  Footnote 8: Histopathology samples used towards IPF diagnosis (if required) will be submitted for central review.	**Section 2.1 Schedule of Assessments During the Core Phase**  Footnote 9: Histopathology samples used towards IPF diagnosis (if available, but these are not required) will be submitted for central review.	*To indicate that histopathology is not required to determine subject eligibility for the Core Phase*
Section 2.1 Schedule of Assessments Footnote 11: The lung HRCT scan will be performed for all subjects within ±2 weeks of the Week 52/PD Visit.	**Section 2.1 Schedule of Assessments During the Core Phase** Footnote 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.	*To emphasize that lung HRCT at Week 52 will include central review.*

<table>
<tr>
<td>Section 2.1 Schedule of Assessments
Not applicable; information added to v4.0 of the protocol.</td>
<td>Section 2.1 Schedule of Assessments During the Core Phase
 
<table>
<tr><td></td><td>Screening[1]</td><td colspan="12">Double-blind Treatment Period</td><td>Safety Follow-up Visit</td></tr>
<tr><td>Trial Visit</td><td></td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td><td>14 4 weeks after last dose of trial drug</td></tr>
<tr><td>Trial Week (W)</td><td>-56 days</td><td>-35 days</td><td>Day 1[2,3]</td><td>W2[4]</td><td>W4</td><td>W6[4]</td><td>W10</td><td>W16</td><td>W22[5]</td><td>W28[3]</td><td>W34[5]</td><td>W40</td><td>W46[5]</td><td>W52/PD[3,6]</td><td>W56</td></tr>
<tr><td>Visit Window (±days)</td><td></td><td></td><td></td><td>(±3)</td><td>(±3)</td><td>(±3)</td><td>(±7)</td><td>(±7)</td><td>(±7)</td><td>(±7)</td><td>(±7)</td><td>(±7)</td><td>(±7)</td><td>(±7)</td><td>(±14)</td></tr>
<tr><td>HBV and HCV serology</td><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>HIV test[21]</td><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Footnote 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.</td>
<td>To indicate that HIV testing is optional at Visit 1</td>
</tr>
<tr>
<td>Section 2.1 Schedule of Assessments
7. Baseline lung HRCT will be performed only if no lung HRCT is available within the last 6 months prior to Screening date and can be performed any time between Screening and Day 1. Results are required to be sent for central review.</td>
<td>Section 2.1 Schedule of Assessments During the Core Phase
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.</td>
<td>To add detail around the baseline lung HRCT</td>
</tr>
<tr>
<td>Not applicable; section added to v4.0 of the protocol.</td>
<td>Section 2.2 Schedule of Assessments During the Extension Phase
See Section 2.2.</td>
<td>To add an optional OLE to the trial</td>
</tr>
<tr>
<td>Section 5.3 Subject Information and Consent
Not applicable; text added to v4.0 of the protocol.</td>
<td>Section 5.3 Subject Information and Consent
Both the Core Phase and the optional open-label Extension Phase will require separate ICFs to be signed by subjects.</td>
<td>To add an optional OLE to the trial</td>
</tr>
</table>

Section 7.1.1 Idiopathic Pulmonary Fibrosis In 2018, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and the Latin American Thoracic Society (ALAT) jointly updated recommendations to reach a consensus for the diagnosis of IPF [Raghu et al., 2018].	**Section 7.1.1 Idiopathic Pulmonary Fibrosis** In 2018, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and the Latin American Thoracic Society (ALAT) jointly updated recommendations to reach a consensus for the diagnosis of IPF and provided additional updates to the guidance in 2022 [Raghu et al., 2018; Raghu et al., 2022].	*To add a citation pertaining to updates to the consensus for the diagnosis of IPF*
Section 7.1.3.4 Clinical Experience As of 10 January 2021, HZN-825 has been studied in humans in a series of 5 Phase 1 clinical trials in healthy subjects and 1 Phase 2a trial in subjects with diffuse cutaneous SSc. Across all trials, HZN-825 was administered to 94 healthy subjects, including 8 elderly subjects, at single doses of up to 1000 mg (i.e., 30, 100, 250, 500 and 1000 mg) and multiple doses of up to 300 mg twice daily (BID) or 600 mg once daily (QD) for 14 days. Overall, HZN-825 was well tolerated and showed similar safety and PK profiles across healthy subjects (including elderly healthy subjects) and subjects with diffuse cutaneous SSc. No gender differences have been observed in systemic exposure or the safety profile. As of 10 January 2021, 47 subjects in Phase 1 trials had received a 600 mg daily dose (38 subjects as 300 mg BID and 9 as 600 mg QD). No SAEs or severe adverse events occurred in Phase 1 studies. One subject experienced adverse events leading to permanent trial drug discontinuation (*Nausea* and *Abdominal pain*) on HZN-825 300 mg BID and midazolam. In a Phase 2a trial that evaluated 32 subjects with diffuse cutaneous SSc, HZN-825 300 mg BID or matching placebo with a randomization ratio of 1:1 was given to subjects in an 8-week double-blind trial, followed by a 16-week open-label extension, to evaluate HZN-825 safety and tolerability, characterize plasma PK, assess potential activity on a series of biomarkers hypothesized to correlate with clinical severity of scleroderma and assess potential clinical benefit. A signal of therapeutic activity was observed in this Phase 2a trial. Treatment with HZN-825 300 mg BID resulted in numerical improvement from Baseline compared with placebo at the end of the 8-week double-blind period and at the end of the	**Section 7.1.3.4 Clinical Experience** HZN-825 has been administered to 102 healthy subjects in 6 completed Phase 1 clinical trials and 31 subjects with diffuse cutaneous SSc in a Phase 2a clinical trial. In clinical trials completed as of 28 February 2022, HZN-825 was well-tolerated and showed similar safety and pharmacokinetic profiles across healthy subjects (including elderly healthy subjects) and subjects with diffuse cutaneous SSc. In the Phase 2a trial, treatment with HZN-825 300 mg twice daily (BID) resulted in numerical improvement from baseline compared with placebo at the end of the 8-week double-blind period and at the end of the 16-week, open-label period based on clinical outcomes, including the modified Rodnan skin score (mRSS), Health Assessment Questionnaire – Disability Index (HAQ-DI) and other components of the Scleroderma Health Assessment Questionnaire (SHAQ), overall disease severity and pruritus [Allanore et al., 2018]. In Phase 1 Trial HZNP-HZN-825-104 in healthy subjects, preliminary data suggested there are no relevant mutual drug-drug interactions between HZN-825 and pirfenidone/nintedanib at clinical doses. The 90% confidence interval (CI) of the geometric least squares mean (GLSM) ratio for both area under the concentration-time curve (AUC) and C_{max} (test vs reference) was within the predefined no-effect bound of (0.70, 1.43). No SAEs or severe adverse events (AEs) occurred in Phase 1 trials. One subject experienced AEs leading to permanent trial drug discontinuation (*Nausea* and *Abdominal pain*) on HZN-825 300 mg BID and midazolam. In the Phase 2a trial, HZN-825 300 mg BID given up to 24 weeks was well-tolerated. During the 8-week double-blind period, the most frequent treatment-emergent adverse	*To update with information from the current Investigator's Brochure (Version 8) and report preliminary results from a Phase 1 drug-drug interaction trial between HZN-825 and pirfenidone or nintedanib to enable the addition of standard-of-care therapy to the current trial*

16-week open-label period based on clinical outcomes, including the modified Rodnan skin score (mRSS), Health Assessment Questionnaire – Disability Index (HAQ-DI) and other components of Scleroderma Health Assessment Questionnaire (SHAQ), overall disease severity (visual analog scale [VAS]) and pruritus (VAS) [Allanore et al., 2018]. In this trial, HZN-825 300 mg BID given up to 24 weeks was well tolerated. During the 8-week double-blind period, the most frequent treatment-emergent adverse events (TEAEs) in the HZN-825 group were headache, diarrhea, nausea and fall.	events (TEAEs) in the HZN-825 group were headache, diarrhea, nausea and fall. Based on safety results to date, orthostatic hypotension is identified as a potential risk of HZN-825 therapy that will continue to be monitored as an AE of special interest (AESI) (Section 9.5.5.1.1.4). Additional and current information regarding the safety of HZN-825 is provided in the current Investigator's Brochure.	
Not applicable; section added to v4.0 of the protocol.	**Section 7.1.3.5 Benefit/Risk Assessment** See Section 7.1.3.5.	*To include information on the potential benefits and risks of HZN-825*
Section 7.2 Rationale for this Trial Not applicable; text added to v4.0 of the protocol.	**Section 7.2 Rationale for this Trial** See last paragraph in Section 7.2.	*To add an optional OLE to the trial*
Section 9.1 Overall Trial Design and Plan This trial will be conducted at approximately 100 sites in the US, Europe, Asia, Australia and New Zealand.	**Section 9.1 Overall Trial Design and Plan** HZNP-HZN-825-303 (HARBOR) will be conducted at approximately 85 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.	*To revise the geographical regions and approximate number of sites in which the trial will be conducted and add an optional OLE to the trial*
Section 9.1 Overall Trial Design and Plan Not applicable; text added to v4.0 of the protocol.	**Section 9.1 Overall Trial Design and Plan** A description of the design of the Extension Phase was added; see **Design of the Extension Phase of the Trial**.	*To add an optional OLE to the trial*

Section 9.1.1 Adjudication Committee Cases of respiratory hospitalizations and acute exacerbations will each be reviewed by an independent adjudication committee in a blinded manner before database lock. Details outlining the responsibilities of the adjudication committee and the parameters related to these events of interest will be included in the adjudication committee charter.	**Section 9.1.1 Adjudication Committee** Cases of respiratory hospitalizations and acute exacerbations will each be reviewed by an independent adjudication committee in a blinded manner before database lock. Details outlining the responsibilities of the adjudication committee and the parameters related to these events of interest will be included in the adjudication committee charter.	*To clarify that the adjudication committee will only pertain to the Core Phase*
Section 9.3.3 Removal of Subjects from Treatment or the Trial 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.	**Section 9.3.3 Removal of Subjects from Treatment or the Trial** 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 discontinuation occurs during the Core Phase) or Week 104 (if discontinuation occurs during the Extension Phase). 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 (if discontinuation occurs during the Core Phase) or Week 104 (if discontinuation occurs during the Extension Phase) assessments. Subjects will be asked to return to the clinic for a Safety Follow-up Visit 4 weeks after the last dose of HZN-825.	*To add text pertaining to the Extension Phase*
Section 9.3.3.1 Removal of Subjects from Treatment • AE. The subject experiences an AE that imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue receiving treatment because of an AE. Subjects who discontinue trial drug due to an AE will remain in the trial unless they withdraw from the trial for another reason.	**Section 9.3.3.1.1 Removal of Subjects from Trial Drug** • AE or clinically significant laboratory/electrocardiogram (ECG) abnormality. The subject experiences an AE or clinically significant laboratory/ECG abnormality that imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue receiving treatment because of an AE or clinically significant laboratory/ECG abnormality. Subjects who discontinue trial drug due to an AE or clinically significant laboratory/ECG abnormality will remain in the trial unless they withdraw from the trial for another reason. In such cases, if situation is not an immediate emergency, the Investigator should contact the trial Medical Monitor.	*To specify that a clinically significant laboratory or ECG abnormality may lead to removal of subjects from treatment*

Section 9.3.3.1 Removal of Subjects from Treatment • Lack of efficacy. Discontinuation of trial drug due to lack of efficacy is at the discretion of the Investigator or subject and may occur if the Investigator determines that trial drug administration is not benefitting the subject. Subjects who discontinue trial drug due to lack of efficacy will remain in the trial for scheduled safety and efficacy assessments through Week 52 unless they also withdraw from the trial for another reason	**Section 9.3.3.1.1 Removal of Subjects from Trial Drug** • Lack of efficacy. Discontinuation of trial drug due to lack of efficacy is at the discretion of the Investigator or subject and may occur if the Investigator determines that trial drug administration is not benefitting the subject. Subjects who discontinue trial drug due to lack of efficacy during the Core Phase will remain in the trial for scheduled safety and efficacy assessments through Week 52 unless they also withdraw from the trial for another reason. Subjects who discontinue trial drug due to lack of efficacy during the Extension Phase will remain in the trial for scheduled safety and efficacy assessments through Week 104 unless they also withdraw from the trial for another reason.	*To add text pertaining to the Extension Phase*
Section 9.3.3.1 Removal of Subjects from Treatment Not applicable; text added to v4.0 of the protocol.	**Section 9.3.3.1.1 Removal of Subjects from Trial Drug** • Restricted medications. Initiation of any therapy prohibited in the trial per Table 9.1 or use of any rescue medications prior to Week 28 may lead to subject discontinuation from treatment (see Section 9.4.9). The Investigator may consult with the trial Medical Monitor before initiation of the restricted medications.	*To add a reason for discontinuation from treatment*
Section 9.3.3.1 Removal of Subjects from Treatment and Section 9.3.3.2 Removal of Subjects from the Trial • Lost to follow-up. The subject does not return to the clinic for scheduled assessments and does not respond to the site's attempts to contact the subject. Subjects who prematurely discontinue trial drug during the Double-blind Treatment Period will be encouraged to continue trial participation in all planned visits, particularly returning for the Week 52/premature discontinuation assessments. Subjects who discontinue trial drug due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained, in addition to being encouraged to continue participation in all planned assessments.	**Section 9.3.3.1.1 Removal of Subjects from Trial Drug and Section 9.3.3.2 Removal of Subjects from the Trial** • Lost to follow-up. The subject does not participate in scheduled assessments and does not respond to the site's attempts to contact the subject. Before the subject is deemed 'lost to follow up,' the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record. Subjects who prematurely discontinue trial drug during the Core Phase will be encouraged to continue trial participation in all planned visits, particularly returning for the Week 52/premature discontinuation assessments. Subjects who prematurely	*To specify that attempts should be made to contact subjects who are initially lost to follow-up and to add text pertaining to the Extension Phase*

	discontinue trial drug during the Extension Phase will be encouraged to continue trial participation in all planned visits, particularly returning for the Week 104/premature discontinuation assessments. Subjects who discontinue trial drug due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained, in addition to being encouraged to continue participation in all planned assessments.	
Not applicable; section added to v4.0 of the protocol.	**Section 9.3.3.1.2 Changes to Background Therapy for IPF** Subjects who change or discontinue standard of care therapy for IPF and/or another agent used to treat IPF should continue treatment with randomized investigational product for the planned duration of the trial unless removal of trial drug is also required due to meeting requirements listed in Section 9.3.3.1.1. The primary reason for change in background therapy should be recorded within the eCRF.	*To provide guidelines for subjects who change or discontinue standard of care therapy for IPF*
Section 9.3.3.2 Removal of Subjects from the Trial • Completed. The subject completed the trial, including the Safety Follow-up Visit (if the subject does not enroll into the extension trial).	**Section 9.3.3.2 Removal of Subjects from the Trial** • Completed. The subject completed the Core Phase, including the Safety Follow-up Visit (if the subject does not enroll into the Extension Phase) or the subject completed the Extension Phase, including the Safety Follow-up Visit.	*To add text pertaining to the Extension Phase*
Section 9.4.1 Treatments Administered On Day 1 of the Double-blind Treatment Period, subjects will be randomized in a 1:1:1 ratio to receive: 1. HZN-825 300 mg QD, or 2. HZN-825 300 mg BID, or 3. Placebo.	**Section 9.4.1 Treatments Administered** During the Core Phase of the trial, on Day 1 of the Double-blind Treatment Period, subjects will be randomized in a 1:1:1 ratio to receive for 52 weeks: 1. HZN-825 300 mg QD, or 2. HZN-825 300 mg BID, or 3. Placebo. During the Extension Phase, all subjects will receive open-label HZN-825 300 mg BID for 52 weeks. The dose for the Extension Phase may be modified based on the results of the Core Phase.	*To add text pertaining to the Extension Phase*

Section 9.4.6 Trial Drug Administration and Timing of Dose for Each Subject Subjects will take 2 tablets of trial drug (HZN-825 150 mg and/or placebo) orally in the morning and evening with a meal. In the event a subject misses a dose, the dose should be taken along with the next planned dose (evening or morning) with a meal.	**Section 9.4.6 Trial Drug Administration and Timing of Dose for Each Subject** Subjects will take 2 tablets of HZN-825 150 mg and/or placebo orally in the morning and evening with a meal in the Core Phase. Subject will take 2 tablets of HZN-825 150 mg orally in the morning and evening with a meal in the Extension Phase. In the event a subject misses a dose, the dose should be taken along with the next planned dose (evening or morning) with a meal such that 4 tablets (up to 600 mg) in total will be taken. Due to a less than dose-proportional increase in HZN-825 systemic exposure, the 600 mg dose taken in the event of a prior missed dose will be considered part of the planned dosing for this trial.	*To add rationale to support the safety of up to a 600 mg dose of HZN-825 and text pertaining to the Extension Phase*
Section 9.4.6.1 Dose Modifications, Interruptions and Delays All dosing instructions are applicable for HZN-825 and placebo administration.	**Section 9.4.6.1 Dose Modifications, Interruptions and Delays** All dosing instructions are applicable for HZN-825 and placebo administration. Any completely missed dose should be recorded on the *Dosing Interruptions* eCRF.	*To specify that any completely missed dose should be recorded on the eCRF*
Section 9.4.7 Method of Assigning Subjects to Treatment Groups A randomization schedule will be generated by an unblinded statistician not otherwise associated with the trial prior to shipment of any trial drug to the clinical sites. On Day 1 of the Double-blind Treatment Period, once all Baseline procedures other than administration of trial drug have been completed, authorized site personnel will use the interactive response technology (IRT) system to randomize the subject. The Investigator or designee will then use the IRT system to obtain dosing information and dispense the appropriate trial drug.	**Section 9.4.7 Method of Assigning Subjects to Treatment Groups** For the Core Phase of the study, a randomization schedule will be generated by an unblinded statistician not otherwise associated with the trial prior to shipment of any trial drug to the clinical sites. On Day 1 of the Double-blind Treatment Period, once all Baseline procedures other than administration of trial drug have been completed, authorized site personnel will use the interactive response technology (IRT) system to randomize the subject. The Investigator or designee will then use the IRT system to obtain dosing information and dispense the appropriate trial drug. All subjects in the Extension Phase will receive open-label HZN-825.	*To add text pertaining to the Extension Phase*

<table>
<tr>
<td>Section 9.4.8 Blinding and Unblinding
An IDMC will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when [redacted]</td>
<td>Section 9.4.8 Blinding and Unblinding
An IDMC will review unblinded safety and efficacy data on a scheduled basis during the Core Phase of the trial. An interim analysis with a futility analysis will be performed when [redacted]</td>
<td>To specify that there will be an interim analysis at Week 28 and that the IDMC will review Core Phase data only</td>
</tr>
<tr>
<td>Section 9.4.8 Blinding and Unblinding
Not applicable; text added to v4.0 of the protocol.</td>
<td>Section 9.4.8 Blinding and Unblinding
The Extension Phase is open-label, and all subjects will receive HZN-825.</td>
<td>To add text pertaining to the Extension Phase</td>
</tr>
<tr>
<td>Section 9.4.9 Concomitant Therapy and Restricted Medications
Table 9.1 → Restricted Medications
<table>
<tr><th>Medication</th><th>Restricted Time Period</th></tr>
<tr><td>Prednisone at steady dose >10 mg/day or equivalent or cyclosporine A</td><td>4 weeks prior to Screening through trial completion
Topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed during the trial.
Short bursts for acute illnesses (asthma, allergic reaction) are permitted.</td></tr>
<tr><td>Other immunosuppressant agents</td><td>Treatment with any other immunosuppressant during the Screening Period through the end of trial participation will require consultation and approval by the trial Medical Monitor.</td></tr>
<tr><td>Commercially approved agent for interstitial lung disease or an investigational agent for any condition</td><td>90 days or 5 half-lives, whichever is longer, prior to Screening through trial completion</td></tr>
<tr><td>Drug/alcohol abuse</td><td>History of abuse within the past 2 years or abuse during trial</td></tr>
<tr><td>Rifampin[1]</td><td>2 weeks prior to dosing through trial completion</td></tr>
<tr><td>OATP inhibitors: clarithromycin, erythromycin and gemfibrozil
P-gp inhibitors: amiodarone, carvedilol, dronedarone, itraconazole, propafenone, quinidine, ranolazine and verapamil
BCRP inhibitor: eltrombopag</td><td>3 days prior to dosing through trial completion</td></tr>
</table>
AUC=area under the concentration-time curve; BCRP=breast cancer resistance protein; CYP=cytochrome P450; INR=international normalized ratio; OATP=organic anion transporter polypeptide; P-gp=P-glycoprotein
For subjects taking warfarin, physicians should monitor their INR, as needed. HZN-825 is a weak inhibitor of CYP2C9, increasing S-warfarin AUC by 23% and R-warfarin AUC by 13% in healthy subjects, with minimal impact on INR (the mean increase in INR at 24 hours post warfarin administration from Baseline was 14.2% without HZN-825 and 16.8% with HZN-825 treatment).
1. Rifampicin is a CYP enzyme inducer and an OATP inhibitor.</td>
<td>Section 9.4.9 Concomitant Therapy and Restricted Medications
Table 9.1 → Restricted Medications
<table>
<tr><th>Medication</th><th>Restricted Time Period</th></tr>
<tr><td>Prednisone at steady dose >10 mg/day or equivalent or cyclosporine[1]</td><td>4 weeks prior to Screening through trial completion
Topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed during the trial.
Short bursts for acute illnesses (asthma, allergic reaction) are permitted.</td></tr>
<tr><td>Other immunosuppressant agents</td><td>Change in treatment regimen or dosage with any other immunosuppressant during the Screening Period through the end of trial participation will require consultation and approval by the trial Medical Monitor.</td></tr>
<tr><td>An investigational agent for any condition</td><td>4 weeks or 5 half-lives, whichever is longer, prior to Screening through trial completion</td></tr>
<tr><td>Drug/alcohol abuse</td><td>History of abuse within the past 2 years or abuse during trial</td></tr>
<tr><td>Rifampin[2]</td><td>2 weeks prior to dosing through trial completion</td></tr>
<tr><td>OATP inhibitors: clarithromycin and gemfibrozil
BCRP inhibitor[3]: eltrombopag</td><td>3 days prior to dosing through trial completion</td></tr>
</table>
BCRP=breast cancer resistance protein; CYP=cytochrome P450; OATP=organic anion transporter polypeptide
1. → Cyclosporine is also an OATP and BCRP inhibitor.
2. → Rifampin is a CYP enzyme inducer and an OATP inhibitor.
3. → Known clinical OATP and BCRP inhibitors include, but are not limited to, the drugs included in this table.</td>
<td>To update restrictions regarding concomitant medications and remove P-gp inhibitors from the list of restricted medications because the strong P-gp transporter inhibitor itraconazole had no impact on HZN-825 exposure at clinically relevant doses in a Phase 1 trial</td>
</tr>
</table>

Section 9.4.9 Concomitant Therapy and Restricted Medications Not applicable; text added in v4.0 of the protocol.	**Section 9.4.9 Concomitant Therapy and Restricted Medications** Caution should be exercised when coadministering HZN-825 with other substrates of CYP2C9 or organic anion transporter (OAT)1/OAT3 that have narrow therapeutic windows. Caution should be observed when coadministering HZN-825 with strong inhibitors of CYP2C9 or CYP2D6. HZN-825 and background therapy drugs (pirfenidone/nintedanib) are not expected to affect each other's exposure (see Section 7.1.3.4).	*To include some additional concomitant medication cautions and information regarding concomitant therapy*
Section 9.4.9 Concomitant Therapy and Restricted Medications In case of a clinically significant deterioration in lung function, initiation of additional therapy is allowed, as described in Table 9.2, after Week 28. Detailed (S)AE information following such events should be recorded in the eCRF.	**Section 9.4.9 Concomitant Therapy and Restricted Medications** In case of a clinically significant deterioration in lung function, initiation of additional therapy or change in dose of background immunosuppressant therapy is allowed after Week 28 following consultation with the trial Medical Monitor. The addition or change of background therapy for IPF treatment due to clinical deterioration will be labeled as "rescue therapy." Detailed (S)AE information following such events should be recorded in the eCRF.	*To delete the table that delineated specific rescue therapy, as such therapy will be determined in consultation with the trial Medical Monitor*
Section 9.4.10 Treatment Compliance Not applicable; text added in v4.0 of the protocol.	**Section 9.4.10 Treatment Compliance** Subjects who are not compliant with trial drug dosing should be counseled about the importance of taking trial drug on time and regularly.	*To stress the importance of compliance with trial drug*
Section 9.5.1.2 6-minute Walk Test 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 ATS guidelines for the 6MWT [Lancaster, 2018].	**Section 9.5.1.2 6-minute Walk Test** 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 ATS guidelines for the 6MWT [Lancaster, 2018; ATS Guidelines, 2002].	*To add a reference to ATS guidelines for the 6MWT*

Section 9.5.1.4 Diffusing Capacity of the Lungs for Carbon Monoxide The site will use its own DLCO equipment and conduct all measurements with the same DLCO equipment in case that several devices are available at the site. Single-breath DLCO measurement will be carried out according to the ATS guideline on DLCO measurements [Graham et al., 2017]. DLCO values will be adjusted for altitude, carboxyhemoglobin and the most recent hemoglobin value. The DLCO assessment should always be performed after the FVC measurement and should always be started approximately the same time each day.	**Section 9.5.1.4 Diffusing Capacity of the Lungs for Carbon Monoxide** The site will use its own DLCO equipment and conduct all measurements with the same DLCO equipment in case that several devices are available at the site. Single-breath DLCO measurement will be performed according to the ATS guideline on DLCO measurements, when possible [Graham et al., 2017]. Refer to the DLCO procedural manual for details. Sites may request, but will not be required, to have subjects attend unscheduled visits for repeat DLCO measurements when the initial measurement has not passed according to DLCO central review quality control criteria. DLCO assessments for determining subject eligibility for the trial can be repeated once during the 35-day Screening window. During the treatment period, repeat measurements should be attempted within 1 week, if possible. DLCO results that do not pass quality control and for which it is not practical to recall the subject to the trial site for a repeat test, Investigators should assess and record within the subject's source documents whether the DLCO performed was valid per the site's standard practices and correlates well with the subject's clinical conditions and previous DLCO results. DLCO values will be adjusted for altitude when necessary, and the most recent hemoglobin value. An adjustment for carboxyhemoglobin will be made if the Investigator determines that the subject may have elevated carboxyhemoglobin. The DLCO assessment should always be performed after the FVC measurement and should always be started approximately the same time each day.	*To clarify language for obtaining DLCO measurement*
Section 9.5.1.6 Patient-reported Outcome Assessments Health outcomes assessments are recommended to be administered with a paper instrument at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments.	**Section 9.5.1.6 Patient-reported Outcome Assessments** Health outcomes assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments.	*To delete mention of paper as all data will be collected electronically for the trial*

Section 9.5.1.6.5 Exit Interviews To understand what subjects perceive as meaningful in terms of change in some of the patient-reported outcome measures, semi-structured qualitative interviews will be conducted by telephone after the Week 52 Visit (trial exit) at 4 to 5 sites (n=20 subjects) across the US. Subjects in the exit interviews will be selected in order to approximate representativeness of the clinical trial population of patients with IPF, with diversity in terms of age, gender, ethnicity, urban/rural practice and geographic area of residence, where possible. The one-on-one, semi-structured, qualitative interviews will provide a greater understanding of the subjects' treatment experience and meaningful change in select patient-reported endpoints.	**Section 9.5.1.6.5 Exit Interviews** To understand what subjects perceive as meaningful in terms of change in some of the patient-reported outcome measures during the Core Phase of the trial, semi-structured qualitative interviews will be conducted by telephone after the Week 52 Visit (trial exit) at 4 to 5 sites (approximately 20 subjects) across the US. Subjects in the exit interviews will be selected in order to approximate representativeness of the clinical trial population of patients with IPF, with diversity in terms of age, gender, ethnicity, urban/rural practice and geographic area of residence, where possible. The one-on-one, semi-structured, qualitative interviews will provide a greater understanding of the subjects' treatment experience and meaningful change in select patient-reported endpoints. These interviews are covered and conducted under a separate protocol, and are not part of the schedule of assessments for HZNP-HZN-825-303.	*To clarify that exit interviews pertain only to the Core Phase and will be covered by a separate protocol*
Section 9.5.2 Pharmacokinetic Measurements If the clinic visit is in the morning, on days when a pre-dose PK sample will be collected (i.e., Weeks 4, 16, 28, 40 and 52), subjects will be instructed to withhold taking trial drug before the visit and drug will be administered in the clinic after the pre-dose PK samples are taken. Time of drug administration in the clinic as well as the most recent dosing time prior to the visit will be recorded; 1 additional PK sample will be collected 2 to 4 hours after dosing in the clinic for during the Week16 and Week 28 Visits. If the clinic visit is in the afternoon, on days when a pre-dose PK sample will be collected (i.e., Weeks 4, 16, 28, 40 and 52), subjects will be instructed to take trial drug before 8 a.m. and record dosing time; 1 PK sample will be collected anytime during the clinic. For the Week 16 and Week 28 Visits, subjects will receive the evening dose during the visit (dosing time to be recorded) if it's at least 8 hours from the morning dosing. An additional PK sample will be collected 2 to 4 hours post-dose; otherwise, subjects will be instructed to take the evening dose at regular dosing time and no post-dose PK sample will be collected.	**Section 9.5.2 Pharmacokinetic Measurements** If the clinic visit is in the morning, on days when a pre-dose PK sample will be collected, subjects will be instructed to withhold taking trial drug before the visit, and drug and a meal will be administered in the clinic after the pre-dose PK samples are taken. Time of drug administration in the clinic as well as the most recent dosing time prior to the visit will be recorded; 1 additional PK sample will be collected 2 to 4 hours after dosing in the clinic during the Week 16, Week 28 and Week 56 Visits. If the clinic visit is in the afternoon, on days when a pre-dose PK sample will be collected, subjects will be instructed to take trial drug before 8 a.m. with a meal and record dosing time; 1 PK sample will be collected anytime during the clinic. For the Week 16, Week 28 and Week 56 Visits, subjects, subjects will receive the evening dose during the visit (dosing time to be recorded) if it is at least 8 hours from the morning dosing. An additional PK sample will be collected 2 to 4 hours post-dose; otherwise, subjects will be instructed to take the evening dose at regular dosing time and no post-dose PK sample will be collected.	*To provide detail regarding taking trial drug with a meal and add Extension Phase time points*

Section 9.5.2 Pharmacokinetic Measurements Not applicable; table added to v4.0 of the protocol.	**Section 9.5.2 Pharmacokinetic Measurements** Table 9.2 was added to show the schedule of pharmacokinetic sample collection.	*To make pharmacokinetic sample collection schedule more reader friendly*
Section 9.5.4 Pharmacodynamic Assessments Blood samples will be taken during the study to evaluate the pharmacodynamic effect of HZN-825. Serum samples will be taken at the following visits: Day 1 (pre-dose), Week 16 (pre-dose), Week 28 (pre-dose) and Week 52 (pre-dose). Samples will be stored frozen for potential analysis of biomarkers of the $LPAR_1$ pathway or IPF disease. All samples will be destroyed after potential biomarkers have been tested or 5 years after the study is complete, whichever comes first. A blood sample will be taken at Day 1 (pre-dose), Week 28 (pre-dose) and Week 52 (pre-dose) for gene expression profiling of peripheral blood mononuclear cells (PBMCs) as it relates to disease biology. Instructions for collection, processing, handling, storing and shipping of samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.	**Section 9.5.4 Pharmacodynamic Assessments** Blood samples will be taken during the trial to evaluate the pharmacodynamic effect of HZN-825. Serum samples will be taken at the following visits: Day 1 (pre-dose), Week 16 (pre-dose), Week 28 (pre-dose), Week 52 (pre-dose), Week 80 (pre dose) and Week 104 (pre-dose). Samples will be stored frozen for potential analysis of biomarkers of the $LPAR_1$ pathway or IPF disease. All samples will be destroyed after potential biomarkers have been tested or 5 years after the trial is complete, whichever comes first. A blood sample will be taken at Day 1 (pre-dose), Week 28 (pre dose), Week 52 (pre-dose), Week 80 (pre-dose) and Week 104 (pre-dose) for gene expression profiling of peripheral blood mononuclear cells (PBMCs) as it relates to disease biology. Instructions for collection, processing, handling, storing and shipping of samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.	*To add Extension Phase time points*
Section 9.5.5.1.1.1 Adverse Event Definition Not applicable; text added in v4.0 of the protocol.	**Section 9.5.5.1.1.1 Adverse Event Definition** A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.	*To add the definition of a suspected adverse reaction and clarify*
Section 9.5.5.1.1.1 Adverse Event Definition Pre-existing conditions that worsen during a trial are to be reported as AEs.	**Section 9.5.5.1.1.1 Adverse Event Definition** Exacerbation of a chronic or intermittent pre-existing condition that worsens in intensity or increases in frequency during a trial is to be reported as an AE.	*To clarify when pre-existing conditions should be reported as AEs*

Section 9.5.5.1.1.4 Adverse Events of Special Interest The following AESI is identified for this trial: • Orthostatic hypotension. The Sponsor will consider an event of orthostatic hypotension if the following definition is met: a reduction of systolic blood pressure by ≥20 mmHg or reduction of diastolic blood pressure by ≥10 mmHg at 1, 5 or 10 minutes in the standing position and associated with symptoms such as lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, presyncope and syncope. Any spontaneously reported signs or symptoms possibly associated with orthostatic hypotension should be reported as AEs. Depending on the timing, nature and severity of these spontaneous AEs, additional investigations will be conducted at the next scheduled visit or at an unscheduled visit, as clinically indicated per the Investigator's judgment. Whenever possible, the following data should be collected: concomitant medications, and blood pressure and heart rate measurements in supine and standing positions. Depending on the severity, plasma glucose level and ECG should be obtained per Investigator's clinical judgment. The protocol-defined orthostatic hypotension assessment procedure (performed as outlined in Section 2.1 on Day 1 and at Weeks 4, 28 and 52/premature discontinuation and is detailed in the Orthostatic Hypotension Assessment Manual in Section 17.9).	**Section 9.5.5.1.1.4 Adverse Events of Special Interest** The following AESI is identified for this trial: • Orthostatic hypotension. The Sponsor will consider an event of orthostatic hypotension if the following definition is met: a reduction of systolic blood pressure by ≥20 mmHg or reduction of diastolic blood pressure by ≥10 mmHg **and** associated with symptoms such as lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, presyncope or syncope. Orthostatic hypotension assessment procedure will be performed during the Core Phase (as outlined in Section 2.1 on Day 1 and at Weeks 4, 28 and 52/premature discontinuation) and the Extension Phase (as outlined in Section 2.2 on Day 1 [Week 52 of Core Phase] and at Weeks 56, 80 and 104/premature discontinuation), as is detailed in the Orthostatic Hypotension Assessment Manual in Section 17.9. If any symptoms occur during the assessment in combination with the blood pressure reductions noted above, they are considered as part of the orthostatic hypotension event and will not be recorded separately as individual AEs. If symptoms are reported by the subject throughout the assessment, without the blood pressure reductions noted above, then the symptoms will be recorded separately as AEs and orthostatic hypotension will not be recorded. Signs and symptoms associated with orthostatic hypotension reported outside of the assessment will be captured as part of spontaneously reported AEs at each visit. Depending on the timing, nature and severity of these spontaneous AEs, additional investigations will be conducted at the next scheduled visit or at an unscheduled visit, as clinically indicated per the Investigator's judgment. Whenever possible, the following data should be collected: concomitant medications, and blood pressure and heart rate measurements in supine and standing positions. Depending on the severity, plasma glucose level and ECG should be obtained per Investigator's clinical judgment.	*To align with language in the updated Orthostatic Hypotension Assessment Manual and add Extension Phase time points*

Section 9.5.5.1.7 Medication Errors All cases of medication errors, which include overdose, will be documented on the AE eCRF in order to capture this important safety information consistently in the database. An AE that leads to or is associated with a medication error, such as an overdose, or an SAE of overdose is to be reported according to the procedures outlined in Sections 9.5.5.1.2 and 9.5.5.1.5, respectively.	**Section 9.5.5.1.7 Medication Errors** An AE or SAE that is associated with a medication error, such as an overdose, is to be reported according to the procedures outlined in Sections 9.5.5.1.2 and 9.5.5.1.5, respectively. All medication errors or overdoses, with or without an AE or SAE, should be recorded as a protocol deviation and reported to the trial Medical Monitor in a timely manner. AEs or SAEs may not occur immediately after the medication error or overdose.	*Clarifying documentation and reporting for medication errors*
Section 9.5.5.2 Pregnancy Reporting Pregnancy testing will be performed for WOCBP. Serum pregnancy tests will be analyzed at a central trial laboratory and the urine pregnancy tests will be performed locally. In addition, at-home pregnancy tests will be completed by WOCBP at Weeks 8, 12, 20, 24, 32, 36, 44 and 48, and results will be reported to the site.	**Section 9.5.5.2 Pregnancy Reporting** Pregnancy testing will be performed for WOCBP. Serum pregnancy tests will be analyzed at a central trial laboratory and the urine pregnancy tests will be performed locally. In addition, at-home pregnancy tests will be completed by WOCBP at Weeks 8, 12, 20, 24, 32, 36, 44 and 48 during the Core Phase and at Weeks 60, 64, 72, 76, 84, 88, 96 and 100 during the Extension Phase, and results will be reported to the site.	*To add Extension Phase time points*
Section 9.5.5.2 Pregnancy Reporting Not applicable; text added in v4.0 of the protocol.	**Section 9.5.5.2 Pregnancy Reporting** Abstinence should only be used as a contraceptive method if it is in line with the subject's usual and preferred lifestyle. Periodic abstinence (calendar, symptothermal, postovulation methods) is not an acceptable method of contraception.	*To include additional clarifications around abstinence*
Section 9.5.5.5 Orthostatic Hypotension Assessment Blood pressure and heart rate will be measured after the subject has rested ≥10 minutes in the supine position and after 1 minute, 5 minutes and 10 minutes in the standing position. Orthostatic hypotension is defined as a reduction of systolic blood pressure by ≥20 mmHg or reduction of diastolic blood pressure by ≥10 mmHg within 10 minutes of standing after being supine, as per orthostatic hypotension assessment document provided by the Sponsor. Symptoms commonly associated with orthostatic hypotension include positional nausea, headache, neck ache, lightheadedness, dizziness, blurred vision, fatigue, palpitations and impaired cognition. Signs and symptoms associated with orthostatic	**Section 9.5.5.5 Orthostatic Hypotension Assessment** Blood pressure and heart rate will be measured after the subject has rested ≥5 minutes in the supine position and after 1 minute and 3 minutes in the standing position, as per the Orthostatic Hypotension Assessment Manual provided by the Sponsor. See Section 9.5.5.1.1.4 for more information on orthostatic hypotension assessment.	*To align with language in the updated Orthostatic Hypotension Assessment Manual and minimize repetition in the protocol*

hypotension will be captured as part of spontaneously reported AEs at each visit.		
Section 9.5.5.7 Electrocardiogram ECG results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated by the Investigator as clinically significant or not clinically significant. A copy of the ECG tracing will remain with the source documents.	**Section 9.5.5.7 Electrocardiogram** ECG results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated by the Investigator as clinically significant or not clinically significant. Any clinically significant abnormal ECG, including a QT interval corrected for heart rate (QTc) >450 ms, should be confirmed by a repeat resting ECG at the same visit. The site personnel should ensure that ECGs are collected after the subject is supine for at least 10 minutes. A copy of the ECG tracing will remain with the source documents.	*To specify that a repeat resting ECG should be conducted if a clinically significant ECG result is obtained*
Section 9.5.5.9 Laboratory Tests for Evaluation Not applicable; text added to v2.0 of the protocol.	**Section 9.5.5.9 Laboratory Tests for Evaluation** Urinalysis test parameters were added (see Section 9.5.5.9).	*To specify the urinalysis laboratory parameters*
Section 9.5.5.9 Laboratory Tests for Evaluation Not applicable; text added in v4.0 of the protocol.	**Section 9.5.5.9 Laboratory Tests for Evaluation** The total blood volume for planned visits through the final safety follow-up visit in the Core Phase is approximately 305 mL. Extension Phase, repeat or unscheduled blood tests performed in individual subjects may add to the total blood volume. Instructions for the collection, handling and analysis of clinical laboratory samples will be provided to the site prior to trial site initiation.	*To include the estimated amount of total blood volume that will be collected from each subject and add text pertaining to the Extension Phase*

Section 9.5.7 Trial Procedures Not applicable; text added in v4.0 of the protocol.	**Section 9.5.7 Trial Procedures** Visits at Weeks 22, 34 and 46 during the Core Phase and at Weeks 74, 86 and 98 during the Extension Phase may be completed at an alternative remote location, e.g., a subject's home, by a visiting home healthcare professional and will be based on local availability and as allowable based on local laws and regulations. Remote locations will be discussed during the consent process per subject's preference and as approved by the Investigator. Site Investigators will have direct awareness and oversight of remote subject visits.	*To allow subject visits to be performed at locations other than the trial site at Weeks 22, 34 and 46 during the Core Phase and at Weeks 74, 86 and 98 during the Extension Phase*
Section 9.6.2 Analysis Sets Three analysis sets will be defined for this trial. The intent-to-treat (ITT) analysis set will include all subjects who are randomized to treatment. This will be the analysis set used for efficacy data analyses and subjects will be analyzed according to the treatment to which they were randomized. The safety analysis set will include all subjects who receive at least 1 dose or partial dose of trial drug. The PK analysis set will include all subjects who receive at least 1 dose or partial dose of HZN-825 and have at least 1 PK sample post HZN-825 treatment.	**Section 9.6.1.2 Analysis Sets** Three analysis sets will be defined for this trial. The full analysis set (FAS) will include all subjects who are randomized to treatment and take at least 1 dose of trial drug. This will be the analysis set used for efficacy data analyses and subjects will be analyzed according to the treatment to which they were randomized. The safety analysis set will include all subjects who receive at least 1 dose or partial dose of trial drug. The PK analysis set will include all subjects who receive at least 1 dose or partial dose of HZN-825 and have at least 1 PK sample post HZN-825 treatment.	*To change the primary analysis set from the intent-to-treat analysis set to the full analysis set*
Section 9.6.3 Primary Efficacy Endpoint Analysis The estimand for the primary efficacy analyses will be constructed to compare the primary endpoint between each dose regimen of HZN-825 and placebo using the treatment policy strategy approach to intercurrent events. All subjects who are randomized will be included in the primary efficacy analyses (ITT analysis set).	**Section 9.6.1.3 Primary Efficacy Endpoint Analysis** The estimand for the primary efficacy analyses will be constructed to compare the primary endpoint between each dose regimen of HZN-825 and placebo using the treatment policy strategy approach to intercurrent events. All subjects who are randomized and take at least 1 dose of trial drug will be included in the primary efficacy analyses (FAS).	*To change the primary analysis set from the intent-to-treat analysis set to the full analysis set*
Section 9.6.4 Secondary Efficacy Endpoint Analyses A Cox proportional hazard model stratified like the previous logistic model with baseline FVC % predicted and treatment group will provide hazard ratio, its 95% CI and p-value to compare each HZN-825 group with the placebo group.	**Section 9.6.1.4 Secondary Efficacy Endpoint Analyses** A Cox proportional hazard model stratified like the previous logistic model with treatment group will provide hazard ratio, its 90% CI and p-value to compare each HZN-825 group with the placebo group.	*To change the CI from 95% to 90% and remove baseline FVC % predicted from the model*

Section 9.6.9 Multiple Comparisons The overall statistical level is α=0.05 (2-sided). An adjustment will be made to account for the futility analysis at the interim analysis. Even though there is no chance to stop the trial at the futility analysis for conclusion of benefit, a small adjustment to the type I error rate with α = 0.001 (2-sided) will be made to account for the unblinded, comparative summary. Therefore, we will use α=0.049 (2-sided) in the final analysis to evaluate the primary and the key secondary endpoints. Because 2 dose regimens of HZN-825 will be compared to placebo in the final analysis, the adjustment for multiplicity will be used for the primary analysis to preserve the family-wise error rate. For the primary endpoint change from Baseline in FVC % predicted at Week 52, a Hochberg testing procedure [Hochberg, 1988] will be used where the larger P-value will be compared at α = 0.049 (2-sided) for the comparisons of HZN-825 BID vs. placebo and HZN-825 QD vs placebo. If statistically significant, then both comparisons will be considered significant. If the larger P-value is not statistically significant, then the smaller P-value will be compared at α = 0.0245 (2-sided). If one or two dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur. If both HZN-825 are statistically significantly better than the placebo for primary efficacy endpoint, the Hochberg testing procedure will be used for the key secondary endpoint with the procedure similar as primary endpoint was performed. If both dose regimens of HZN-825 for the key secondary endpoint are considered significant, subsequent secondary endpoints will be tested sequentially within each dose regimen in the order shown in Section 9.6.1.2, using α=0.0245 (2-sided) in a sequential testing procedure. Although p-values will be provided for exploratory endpoints, they will not be used for inferential purposes.	**Section 9.6.1.9 Multiple Comparisons** The overall statistical level is α=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, α=0.10 (2-sided) will be used in the final 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.	*To update values for significance level due to updated overall significance level (alpha = 0.10,2-sided) and specify that p-values for other secondary endpoints will not be used for inferential purposes*

Section 16 References Not applicable; reference added to v4.0 of the protocol.	**Section 16 References** ATS Guidelines. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7. Erratum in: Am J Respir Crit Care Med. 2016;193(10):1185. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205(9):e18-47.	*To add a reference to ATS guidelines for the 6MWT and the citation pertaining to updates to the consensus for the diagnosis of IPF*
Section 16 References Hochberg Y. A Sharper Bonferroni Procedure for Multiple Test of Significance. Biometrika 75 (4), 1988;800-802.	**Section 16 References** This reference was deleted in v4.0 of the protocol.	*To delete a reference because of the change in testing procedure for multiple comparisons*
Section 17 APPENDICES Not applicable; text added in v4.0 of the protocol.	**Section 17 APPENDICES** Versions of the assessment instruments are provided in the appendices as examples based on the versions available at the time of protocol publication and may differ from the assessment instruments actually administered in the trial in the event that additional validated versions become available.	*To alert trial personnel to the fact that the actual assessment instruments used may differ from those in the protocol*
Appendix 17.1 Administrative Appendix Medical Monitor → [redacted] MD → Medical Director, Clinical Development → Horizon Therapeutics U.S.A., Inc. → 1 Horizon Way → Deerfield, IL 60015 → Mobile telephone number: [redacted] → Email: [redacted]	**Appendix 17.1 Administrative Appendix** Medical Monitor → [redacted] MBBS, MD → Senior Medical Director, Clinical Development → Horizon Therapeutics U.S.A., Inc. → 1 Horizon Way → Deerfield, IL 60015 → Mobile telephone number: [redacted] → Email: [redacted]	*To change the Medical Monitor*

Appendix 17.1 Administrative Appendix Sponsor Contact for Serious Adverse Event Reporting → Horizon Therapeutics U.S.A., Inc.¶ → US Fax: 800-860-7836¶ → Email: clinicalsafety@horizontherapeutics.com¶	**Appendix 17.1 Administrative Appendix** Sponsor Contact for Serious Adverse Event Reporting → Horizon Therapeutics U.S.A., Inc.¶ → US Fax: 800-860-7836¶ → Ex US Fax: +1-224-855-5055¶ → Email: clinicalsafety@horizontherapeutics.com¶	*To add an ex US fax number*
Appendix 17.7 SF-12® Health Survey (SF-12) This appendix included an old sample of this instrument.	**Appendix 17.7 SF-12® Health Survey (SF-12)** This appendix was updated with a sample US Version 2.0.	*To update to the most current version of the SF-12*
Appendix 17.9 Orthostatic Hypotension Assessment Manual This appendix included Version 1.0, Dated 07 Dec 2020.	**Appendix 17.9 Orthostatic Hypotension Assessment Manual** This appendix was updated with Version 2.0, Dated 28 Feb 2022, that changed the timing and frequency of blood pressure and heart rate recordings and removed the Valsalva provocation test and patient-reported outcome assessment.	*To align process with current guidelines, to make the process more understandable and improve the method of data collection*

SUMMARY OF CHANGES
Protocol HZNP-HZN-825-303
Version 3.0 Amendment 2, incorporating Protocol Version 2.0

Key additions, revisions and clarifications to Version 2.0 of the protocol include:

- Changing the timing of interim (futility) analyses to occur [redacted]
- Further clarifying in the Schedule of Assessment table that pharmacogenetic assessment and sampling is optional.
- Providing details on the IDMC's role in recommending dose selection and trial continuation.
- Modifying the statistical analysis to reduce nominal alpha spending at interim (futility) analysis and increase power for final analysis. The Hochberg testing procedure will be used.
- Changing the screening period to 35 days to allow additional flexibility.
- Clarifying that unfasted glucose testing is included in the planned standard chemistry panel utilized by the central lab.
- Clarifying the methods of contact the Investigator can use to report pregnancies to the Sponsor.
- Clarifying that monitoring should continue to the conclusion of pregnancy.

Changes considered not key, minor wording changes and correction of minor typographical errors are not detailed below.

SUMMARY TABLE OF CHANGES
Protocol Version 2.0 (02 August 2021) to Protocol Version 3.0, Amendment 2 (11 October 2021)

Text Version 2.0, Amendment 1 02 August 2021	Amended Text Version 3.0, Amendment 2 11 October 2021	Reason for Change
Synopsis– Trial Design, Section 9.1 Overall Trial Design and Plan, A futility analysis will be performed [redacted] and these unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC).	**Synopsis– Trial Design, Section 9.1 Overall Trial Design and Plan,** A futility analysis will be performed [redacted] and these unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC).	*To ensure sufficient safety and efficacy data are available to the IDMC to inform dose selection and trial continuation*
Synopsis– Criteria for Evaluation Blood samples for HZN-825 and metabolite(s) PK assessment, pharmacodynamic markers and pharmacogenetic assessment (for drug metabolizing enzymes and/or transporters) will be collected.	**Synopsis– Criteria for Evaluation** Blood samples for HZN-825 and metabolite(s) PK assessment, pharmacodynamic markers and optional pharmacogenetic assessment (for drug metabolizing enzymes and/or transporters) will be collected.	*To further clarify that a blood sample for pharmacogenetic assessment is optional*
Synopsis– Efficacy, Section 9.6.8 Interim Analyses [redacted]	**Synopsis– Efficacy, Section 9.6.8 Interim Analyses** [redacted]	*To ensure sufficient safety and efficacy data are available to the IDMC to inform dose selection and trial continuation*

Synopsis– Efficacy, Section 9.6.8 Interim Analyses Not applicable (new addition in Amendment 2)	**Synopsis– Efficacy, Section 9.6.8 Interim Analyses** 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 studies. For additional details, please refer to the IDMC charter for this study.	*To provide details regarding IDMC process per IDMC charter*
Synopsis– Efficacy Because 2 dose regimens of HZN-825 will be compared to placebo, an adjustment for multiple comparisons will be made and the primary analysis will be interpreted using α=0.025, 2-sided, for each comparison. An additional adjustment will be made to account for the futility analysis. Even though there is no chance to stop the trial at the futility analysis for conclusion of benefit, a small adjustment to the Type I error rate will be made to account for the unblinded, comparative summary. Adjusting the Type I error rate by 0.001 for each comparison of an HZN-825 dose regimen to placebo results in the final analysis using α=0.024 to compare each HZN-825 dose regimen to placebo. Secondary endpoints for comparing each HZN-825 dose regimen to placebo will be tested in the order presented above. Each endpoint will be compared to placebo within a dose regimen only if the primary and all prior secondary endpoints first show statistical significance.	**Synopsis– Efficacy** The overall statistical level is α=0.05 (2-sided). Because 2 dose regimens of HZN-825 will be compared to placebo, a Hochberg testing procedure will be used for multiple comparison [Hochberg, 1988]. An additional adjustment will be made to account for the futility analysis. Even though there is no chance to stop the trial at the futility analysis for conclusion of benefit, a small adjustment to the type I error rate (0.001, 2-sided) will be made to account for the unblinded, comparative summary. Therefore, we will use α=0.049 (2-sided) in the final analysis. The Hochberg testing procedure will be used for the primary endpoint first. If one or two dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur. If both HZN-825 are statistically significantly better than the placebo for primary efficacy endpoint, the Hochberg testing procedure will be used for the key secondary endpoint similar as the primary endpoint was performed. If both dose regimens of HZN-825 for the key secondary endpoint are considered significant, subsequent secondary endpoints will be tested sequentially within each dose regimen in the order as above, using α=0.0245 (2-sided) in a sequential testing procedure.	*To reduce the nominal alpha spending at interim (futility) analyses and increase the power for the final analysis* *The Hochberg method, which is a more powerful test for the primary endpoint, is used in lieu of Graphic method.*

Synopsis– Sample Size Estimate Assuming a clinically important difference between HZN-825 and placebo is 4% and a common standard deviation is 9%, a sample size of 120 subjects per treatment group will provide 88% power to detect a clinically important difference between each posology of HZN-825 and placebo at a significance level of 0.024, 2-sided.	**Synopsis– Sample Size Estimate** Assuming a clinically important difference between HZN-825 and placebo is 4% and a common standard deviation is 9%, a sample size of 120 subjects per treatment group will provide 88% power to detect a clinically important difference between each posology of HZN-825 and placebo at a significance level of 0.0245, 2-sided.	*To reduce the nominal alpha spending at interim (futility) analyses and increase the power for the final analysis*
Section 2.1 Schedule of Assessments Screening period is 28 days.	**Section 2.1 Schedule of Assessments** Screening period is 35 days.	*To provide additional flexibility in the screening period*
Section 2.1 Schedule of Assessments Pharmacogenetic sample[24]	**Section 2.1 Schedule of Assessments** Pharmacogenetic sample (optional)[24]	*To further clarify that a blood sample for pharmacogenetic assessment is optional*
Section 2.1 Schedule of Assessments, Section 9.5.5.9 Laboratory Test for Evaluation Chemistry parameters to be evaluated include total protein, albumin, sodium, phosphate, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase, uric acid, lactate dehydrogenase; liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, total bile acid, total bilirubin, conjugated and unconjugated bilirubin, if applicable).	**Section 2.1 Schedule of Assessments, Section 9.5.5.9 Laboratory Test for Evaluation** Chemistry parameters to be evaluated include 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).	*To clarify that unfasted glucose testing is included in the planned standard chemistry panel utilized by the central lab*

Section 9.4.8 Blinding and Unblinding, Section 9.6.8 Interim Analyses A futility analysis will be performed when [redacted]	**Section 9.4.8 Blinding and Unblinding, Section 9.6.8 Interim Analyses** A futility analysis will be performed when [redacted]	*To ensure sufficient safety and efficacy data are available to the IDMC to inform dose selection and trial continuation*
Section 9.5.5.2 Pregnancy Reporting The Investigator should report pregnancies to the Sponsor within 24 hours by submitting the completed pregnancy report form within 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see Section 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy.	**Section 9.5.5.2 Pregnancy Reporting** The Investigator should report pregnancies to the Sponsor within 24 hours by submitting the completed pregnancy report form by email to clinicalsafety@horizontherapeutics.com, fax or telephone within 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see Section 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy.	*To clarify the contact methods the Investigator can use to report pregnancies to the Sponsor*
Section 9.5.5.2 Pregnancy Reporting If pregnancy continues and the subject signs the pregnancy consent form, the subject will be contacted 2 weeks after her calculated delivery time to provide information about the outcome of the pregnancy and the well-being of the child. A final contact will be made 8 weeks after delivery, when the subject will again be asked about the well-being of the child.	**Section 9.5.5.2 Pregnancy Reporting** If pregnancy continues and the subject signs the pregnancy consent form, monitoring should also continue to the conclusion of the pregnancy.	*To provide clarity for pregnancy reporting to ensure monitoring continues throughout the pregnancy*

Section 9.6.9 Multiple Comparisons Because 2 dose regimens of HZN-825 will be compared to placebo, an adjustment for multiple comparisons will be made, and the primary analysis will be interpreted using α=0.025, 2-sided, for each comparison. An additional adjustment will be made to account for the futility analysis. Even though there is no chance to stop the trial at the futility analysis for conclusion of benefit, a small adjustment to the Type I error rate will be made to account for the unblinded, comparative summary. Adjusting the Type I error rate by 0.001 for each comparison of a dose regimen of HZN-825 to placebo results in the final analysis using α=0.024 to compare each dose regimen of HZN-825 to placebo. Secondary endpoints for comparing each dose to placebo will be tested in the order presented in Section 9.6.1.2. Each endpoint will be compared to placebo within a dose regimen only if the primary and all prior secondary endpoints first show statistical significance. The primary and first secondary endpoints for comparing the 2 dose regimens will be tested as follows: • If the primary endpoint is not significant comparing either of the 2 dose regimens of HZN-825 to placebo, no further alpha-protected testing will be reported. • If the primary endpoint is significant comparing each of the 2 dose regimens of HZN-825 to placebo, the first secondary endpoint will be tested, comparing each dose regimen to placebo, using the Holm procedure with equal weighting, first rejecting the null hypothesis associated with the smaller p-value if that p-value is ≤0.024, and then rejecting the null hypothesis associated with the larger p-value if that p-value is ≤0.048. o If statistical significance is shown for both dose regimens, subsequent secondary endpoints will be	**Section 9.6.9 Multiple Comparisons** The overall statistical level is α=0.05 (2-sided). An adjustment will be made to account for the futility analysis at the interim analysis. Even though there is no chance to stop the trial at the futility analysis for conclusion of benefit, a small adjustment to the type I error rate with α = 0.001 (2-sided) will be made to account for the unblinded, comparative summary. Therefore, we will use α=0.049 (2-sided) in the final analysis to evaluate the primary and the key secondary endpoints. Because 2 dose regimens of HZN-825 will be compared to placebo in the final analysis, the adjustment for multiplicity will be used for the primary analysis to preserve the family-wise error rate. For the primary endpoint change from Baseline in FVC % predicted at Week 52, a Hochberg testing procedure [Hochberg, 1988] will be used where the larger P-value will be compared at α = 0.049 (2-sided) for the comparisons of HZN-825 BID vs. placebo and HZN-825 QD vs placebo. If statistically significant, then both comparisons will be considered significant. If the larger P-value is not statistically significant, then the smaller P-value will be compared at α = 0.0245 (2-sided). If one or two dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur . If both HZN-825 are statistically significantly better than the placebo for primary efficacy endpoint, the Hochberg testing procedure will be used for the key secondary endpoint with the procedure similar as primary endpoint was performed. If both dose regimens of HZN-825 for the key secondary endpoint are considered significant, subsequent secondary endpoints will be tested sequentially within each dose regimen in the order shown in Section 9.6.1.2, using α=0.0245 (2-sided) in a sequential testing procedure.	*To reduce the nominal alpha spending at interim (futility) analyses and increase the power for the final analysis* *The Hochberg method, which is a more powerful test for the primary endpoint, is used in lieu of Graphic method.*

tested sequentially within each dose regimen in the order shown above, using α=0.024 in a sequential testing procedure. • If the primary endpoint is significant comparing exactly 1 of the 2 dose regimens of HZN-825 to placebo, the secondary endpoint for that dose will then be tested at α=0.024. o If the comparison of that secondary endpoint is significant at α=0.024, the primary endpoint for comparing the other dose regimen to placebo will then be tested at α=0.048. o If that comparison also shows significance, the secondary endpoint for comparing the other dose regimen to placebo will be tested at α=0.048. o If this comparison also shows significance, subsequent secondary endpoints will be tested sequentially within each dose regimen in the order shown above, using α=0.024 in a sequential testing procedure. The multiple comparisons procedure described above can be written as a graphical procedure [Bretz et al., 2009] and, therefore, controls the Type I error rate in the strong sense for the family of all primary and secondary endpoints, comparing both dose regimens of HZN-825 to placebo.		

SUMMARY OF CHANGES
Protocol HZNP-HZN-825-303
Version 2.0 Amendment 1, incorporating Protocol Version 1.0

Key additions, revisions and clarifications to Version 1.0 of the protocol include:

- Updating the development phase of the trial from 2b/3 to 2b.
- Specifying evaluation of the proportion of subjects with decline in FVC % predicted ≥10% from Baseline after 52 weeks of treatment as the first secondary objective.
- Changing the definition of progression-free survival (PFS) to exclude lung transplant and moving the PFS objective to be the last secondary objective pertaining to efficacy.
- Changing some secondary and exploratory endpoints from analysis of rate to analysis of time to event and updating the description of the statistical analyses of these endpoints accordingly.
- Updating the order of trial endpoints to be consistent with changes to the objectives.
- To minimize the amount of missing data, emphasizing that subjects who prematurely discontinue trial drug will be asked to remain in the trial, participating in the scheduled trial visits through Week 52.
- Removing the specification that the 6-Minute Walk Test (6MWT) will be performed at selected sites, as it will be performed at all sites.
- Clarifying the assessments (cardiac, pulmonary and neurologic assessments) to be included as part of the physical examination.
- Changing fasting glucose to be analyzed at the same time points as lipid profile and that subjects should fast at least 8 hours before collection of samples for glucose and lipids.
- Deleting erythrocyte sedimentation rate.
- Specifying that an independent adjudication committee will review cases of respiratory hospitalizations and acute exacerbations.
- Excluding subjects with moderate to severe hepatic impairment based on Child-Pugh score.
- Specifying that trial drug should be taken with a meal to achieve sufficient targeted drug exposure.
- Allowing for an echocardiogram that has been performed within the 3 months prior to Baseline to serve as the Baseline echocardiogram if the subject has been clinically stable because some countries have annual echocardiograms as standard of care.
- Adding organic anion transporter polypeptide (OATP) inhibitors, P-glycoprotein (P-gp) inhibitors and a breast cancer resistance protein (BRCP) inhibitor as restricted medications.
- Adding definitions of women of childbearing potential (WOCBP), postmenopausal women and fertile men to exclusion criterion 8.

- Changing pregnancy testing to every 4 weeks, adding specifics regarding pregnancy outcome follow-up and adding examples of highly effective contraceptive methods.
- Adding a statement that development safety update reports will be submitted to countries and territories as required.
- Adding the definition of "end-of-trial."
- Clarifying that unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management unless other select Horizon personnel need to be unblinded.
- Providing guidance regarding restarting trial drug after a subject experiences clinically significant orthostatic hypotension.
- Providing regional addresses for the central safety laboratory.
- Removing long-term survival follow-up.
- Clarifying serious adverse event (SAE) reporting requirements.
- Adding reasons that a treatment group or the trial may be discontinued.
- Indicating Investigator discretion in repeat of spirometry prior to rescue medication.
- Clarifying that, during the Screening Period, cyclophosphamide and prednisone >10 mg/day are not permitted for 4 weeks prior to Screening and throughout Screening.
- Clarifying that an abnormal test during Screening may be repeated once during the Screening Period.
- Adding an appendix regarding hospitalization due to respiratory distress.

Changes considered not key, minor wording changes and correction of minor typographical errors are not detailed below.

SUMMARY TABLE OF CHANGES
Protocol Version 1.0 (17 March 2021) to
Protocol Version 2.0, Amendment 1 (02 August 2021)

Text Version 1.0 17 March 2021	Amended Text Version 2.0, Amendment 1 02 August 2021	Reason for Change
Title Page Any death, life-threatening event or other serious adverse event experienced by a subject during the course of the trial, whether or not judged drug-related, must be reported within 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF). If unable to access the eCRF, the event must be reported by submitting the completed Serious Adverse Event Form via email or fax to the contacts provided below.	**Title Page** Any death, life-threatening event or other serious adverse event experienced by a subject during the course of the trial, whether or not judged drug-related, must be reported immediately, without undue delay but not later than 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF). If unable to access the eCRF, the event must be reported by submitting the completed Serious Adverse Event Form via email or fax to the contacts provided below.	*To clarify SAE reporting requirements*
Title Page and Synopsis Phase: 2b/3	**Title Page and Synopsis** Phase: 2b	*To update the development phase of the trial*
Synopsis – Secondary Objectives and Section 8.2 Secondary Objectives <u>Secondary Objectives</u> 1. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the composite endpoint of progression-free survival (PFS), where progression includes death, lung transplant or decline in FVC ≥10% from Baseline after 52 weeks of treatment. 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.	**Synopsis – Secondary Objectives and Section 8.2 Secondary Objectives** <u>Secondary Objectives</u> 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. 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.	*To specify the proportion of subjects with decline in FVC % predicted ≥10% from Baseline after 52 weeks of treatment as the first secondary*

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 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. Assess safety and tolerability of HZN-825 based on adverse events (AEs), serious adverse events (SAEs) and adverse event of special interest (AESI). 8. Evaluate the pharmacokinetics (PK) of HZN-825 and metabolite(s).	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 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 based on adverse events (AEs), serious adverse events (SAEs) and adverse event of special interest (AESI). 9. Evaluate the pharmacokinetics (PK) of HZN-825 and metabolite(s).	*objective, change the definition of PFS to exclude lung transplant and move the PFS objective to be the last secondary objective pertaining to efficacy*
Synopsis – Trial Design and Section 9.1 Overall Trial Design and Plan The trial 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 return to the clinic for trial visits at Week 4 and every 6 weeks thereafter until Week 52. There will be remote (telephone) visits at Weeks 2 and 6 to monitor safety. Subjects who complete the 52-week Double-blind Treatment Period may be eligible to enter a 52-week extension trial (HZNP-HZN-825-304). If the subject does not enroll into the extension trial, a Safety Follow-up Visit will occur 4 weeks after the last dose of trial drug.	**Synopsis – Trial Design and Section 9.1 Overall Trial Design and Plan** The trial 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 return to the clinic for 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 enter a 52-week extension trial (HZNP-HZN-825-304). If the subject does not enroll into the extension trial, 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.	*To minimize the amount of missing data, emphasizing that subjects who prematurely discontinue trial drug will be asked to remain in the trial, participating in the scheduled trial visits*

		through Week 52
Synopsis – Trial Design, Section 9.1 Overall Trial Design and Plan and Section 9.4.8 Blinding and Unblinding The IDMC charter will include processes to unblind select Horizon personnel who are not directly involved with the trial conduct to assess unforeseen issues that may involve subject safety or dose selection; otherwise, unblinded information will be restricted to IDMC members who are not involved in other aspects of the trial.	**Synopsis – Trial Design, Section 9.1 Overall Trial Design and Plan and Section 9.4.8 Blinding and Unblinding** The IDMC charter will include processes to unblind select Horizon personnel who are not directly involved with the trial conduct to assess unforeseen issues that may involve subject safety or dose selection; otherwise, unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management.	*To clarify that unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management unless other select Horizon personnel need to be unblinded*

Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria 8. Women of childbearing potential or male subjects not agreeing to use highly effective method(s) of birth control throughout the trial and for 1 month after last dose of trial drug. Male subjects must refrain from sperm donation and females from egg/ova donation for this same time period.	**Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria** 8. Women of childbearing potential (WOCBP) or male subjects not agreeing to use highly effective method(s) of birth control throughout the trial and for 1 month after last dose of trial drug. Male subjects must refrain from sperm donation and females from egg/ova donation for this same time period. Women are considered of childbearing potential if they are not postmenopausal and not surgically sterile (documented bilateral salpingectomy, bilateral oophorectomy or hysterectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.	*To define WOCBP, post-menopausal women and fertile men*
Synopsis Not applicable (criterion added to v2.0 of the protocol)	**Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria** 20. Moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment according to the Child-Pugh scoring system.	*To exclude subjects with moderate to severe hepatic impairment*
Synopsis– Dose Regimen/Route of Administration Subjects will take 2 tablets of trial drug orally in the morning and evening with food.	**Synopsis– Dose Regimen/Route of Administration** Subjects will take 2 tablets of trial drug orally in the morning and evening with a meal.	*"With food" could be interpreted as dosing with a snack, which is not sufficient for targeted drug exposure*

Synopsis – Statistical Analyses and Section 9.6.1.2 Secondary Efficacy Endpoints and Section 9.6.1.3 Exploratory Endpoints Secondary Efficacy Endpoints 1. Proportion of subjects meeting the composite endpoint of PFS at Week 52, where progression includes death, lung transplant or decline in FVC ≥10%. 2. Change from Baseline in the 6MWT results to Week 52. 3. Change from Baseline in K-BILD scores to Week 52. 4. Change from Baseline in L-IPF scores to Week 52. 5. Change from Baseline in LCQ scores to Week 52. 6. Rate of hospitalization due to respiratory distress up to Week 52. Exploratory Endpoints 1. [redacted] 2. 3. 4. 5. 6. Rate of mortality due to respiratory deterioration up to Week 52. 7. [redacted] (Remaining exploratory endpoints are not shown because no change from v1.0 to v2.0 of the protocol.)	**Synopsis – Statistical Analyses and Section 9.6.1.2 Secondary Efficacy Endpoints and Section 9.6.1.3 Exploratory Endpoints** Secondary Efficacy Endpoints 1. Proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52. 2. Change from Baseline in the 6MWT results to Week 52. 3. Change from Baseline in K-BILD scores to Week 52. 4. Change from Baseline in L-IPF scores to Week 52. 5. Change from Baseline in LCQ scores to Week 52. 6. Time to first hospitalization due to respiratory distress from Baseline up to Week 52. 7. Time to first onset of the composite endpoint of PFS from Baseline up to Week 52, where progression includes decline in FVC % predicted ≥10% or death. Exploratory Endpoints 1. [redacted] 2. 3. 4. 5. 6. Time to death due to respiratory deterioration from Baseline up to Week 52. 7. [redacted]	*To specify the proportion of subjects with decline in FVC % predicted ≥10% from Baseline after 52 weeks of treatment as the first secondary endpoint, change the definition of PFS to exclude lung transplant, move the PFS endpoint to be the last secondary efficacy endpoint and change some secondary and* [redacted]

Synopsis – Statistical Analyses and Section 9.6.4 Secondary Efficacy Endpoint Analyses The first ranked secondary endpoint will be the proportion of subjects meeting the composite endpoint of PFS (including death, lung transplant or decline in FVC ≥10%). The PFS endpoint will be analyzed using a stratified analysis, with stratification by factors used for stratifying the randomization. Within each of the 4 resulting strata, data will be summarized and the strata will be combined into a single test statistic using Cochran-Mantel-Haenszel weighting. Statistical significance for the PFS endpoint will only be concluded if statistical significance is achieved for the primary efficacy endpoint.	**Synopsis – Statistical Analyses and Section 9.6.4 Secondary Efficacy Endpoint Analyses** The key secondary endpoint will be the proportion of subjects with decline in FVC % predicted ≥10% from Baseline at Week 52 and will be analyzed using a logistic regression model with baseline FVC % predicted, treatment group and stratified by factors used for stratifying the randomization. The logistic model will provide odds ratio, its 95% CI and p-value for comparing each HZN-825 group with the placebo group. Statistical significance for the key secondary endpoint will only be concluded if statistical significance is achieved for the primary efficacy endpoint.	*To specify the proportion of subjects with decline in FVC % predicted ≥10% from Baseline after 52 weeks of treatment as the first secondary endpoint*

Section 2.1 Schedule of Assessments

2.1 → Schedule of Assessments¶

Trial Visit	Screening[2]		Double-blind Treatment Period[2]												Safety Follow-up 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	-28 days	Day 1[2,3]	W2[2,3]	W4	W6[2,3]	W10	W16	W22	W28	W34	W40	W46	W52/PD[4,6]	W56	
Visit Window (±days)				(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	
Informed consent[2,6]	X															
HRCT sent to central review[2,7]	X															
Histopathology sent to central review (as available)[2,8]	X															
Review eligibility criteria		X	X													
Demographics		X														
Medical history[2,6]		X	X													
Weight		X	X											X		
Height		X														
Randomization[2,9]			X													
Trial drug dispensing			X		X		X	X	X	X	X	X	X	X[10]		
Treatment compliance				X	X	X	X	X	X	X	X	X	X	X		
FVC % predicted/spirometry		X	X		X			X		X		X		X		
Titrated oxygen requirement			X					X		X		X		X		
6MWT (if applicable; selected site only)			X					X		X				X		
Lung HRCT[2,11]														X[11]		
DLCO[2,12]		X	X					X		X		X		X		

Section 2.1 Schedule of Assessments (continued)

Trial Visit	Screening[2]		Double-blind Treatment Period[2]												Safety Follow-up 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	-28 days	Day 1[2,3]	W2[2,3]	W4	W6[2,3]	W10	W16	W22	W28	W34	W40	W46	W52/PD[4,6]	W56	
Visit Window (±days)				(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	
Patient-reported outcome assessments																
L-IPF, K-BILD, LCQ, SF-12			X[11]					X		X		X		X		
Anchor questions																
FVC (last week)			X					X		X		X		X		
FVC (change since start of trial)										X				X		
Pregnancy test[13]		X	X		X			X		X		X		X	X	
Physical examination[14]		X	X							X				X	X	
Vital signs, including pulse oximetry[15]		X	X		X		X	X	X	X	X	X	X	X	X	
Orthostatic hypotension assessment			X		X					X				X		
12-lead electrocardiogram[16]		X	X		X			X		X				X		
Echocardiogram[16]		X												X		
Laboratory evaluations																
Chemistry and hematology[17,18]		X	X		X		X	X	X	X	X	X	X	X	X	
Fasting glucose and lipids[19]			X							X				X		
~~hsCRP~~			X							X				X		
Hematology		X	X		X		X	X	X	X	X	X	X	X	X	

Section 2.1 Schedule of Assessments

2.1 Schedule of Assessments

Trial Visit	Screening[1]		Double-blind Treatment Period												Safety Follow-up 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	-28 days	Day 1[2,3]	W2[4]	W4	W6[4]	W10	W16	W22	W28[3]	W34	W40	W46	W52/PD[3,6]	W56	
Visit Window (±days)				(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	
Informed consent[6]	X															
Lung HRCT central review[7]	X															
Histopathology central review (as available)[8]	X															
Review eligibility criteria		X	X													
Demographics		X														
Medical, IPF and substance abuse history		X	X													
Weight		X	X							X				X		
Height		X														
Randomization[9]			X													
Trial drug dispensing			X		X		X	X	X	X	X	X	X	X[10]		
Treatment compliance				X	X	X	X	X	X	X	X	X	X	X		
FVC % predicted/spirometry		X	X		X			X		X		X		X		
Titrated oxygen requirement			X					X		X		X		X		
6MWT			X					X		X				X		
Lung HRCT														X[11]		
DLCO[12]		X	X					X		X		X		X		

Section 2.1 Schedule of Assessments (continued)

Trial Visit	Screening[1]		Double-blind Treatment Period												Safety Follow-up 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	-28 days	Day 1[2,3]	W2[4]	W4	W6[4]	W10	W16	W22	W28[3]	W34	W40	W46	W52/PD[3,6]	W56	
Visit Window (±days)				(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)	
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[13]		X	X		X			X		X		X		X	X	
Physical examination[14]		X	X							X				X	X	
Vital signs, including pulse oximetry[15]		X	X		X		X	X	X	X	X	X	X	X	X	
Orthostatic hypotension assessment			X		X					X				X		
12-lead electrocardiogram[16]		X	X		X			X		X				X		
Echocardiogram[16]		X												X		
Laboratory evaluations																
Chemistry and hematology[17,18]		X	X		X		X	X	X	X	X	X	X	X	X	
Fasting glucose and lipids[19]			X							X				X		
~~hsCRP~~			X							X				X		
Hematology		X	X		X		X	X	X	X	X	X	X	X	X	

To: clarify that an abnormal test during Screening may be repeated once during the Screening Period; change pregnancy testing to every 4 weeks and fasting glucose to be analyzed at the same time points as lipid profile and that subjects should fast at least 8 hours before collection of samples for glucose and lipids; delete erythrocyte sedimentation rate from the protocol; allow for an echocardiogram that has been performed within the 3 months prior

Section 2.1 Schedule of Assessments (continued)

Trial Visit	Screening[1]		Double-blind Treatment Period												Safety Follow-up 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	-28 days	Day 1 [2,3]	W2 [4]	W4	W6 [4]	W10	W16	W22	W28 [3]	W34	W40	W46	W52/PD [4,5]	W56
Visit Window (±days)				(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±14)
Urinalysis		X	X		X		X	X	X	X	X	X	X	X	X
HBV and HCV serology		X													
Adverse event assessment [20]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concom. medications [21]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK samples [22]			X		X		X	X		X		X		X	
Pharmacodynamic serum sample (collect pre-dose) [23]			X					X		X				X	
Pharmacogenetic sample [24]			X												
PBMC sample [25]			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; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; IPF=idiopathic pulmonary fibrosis; LCQ=Leicester Cough Questionnaire; L-IPF=Living with IPF; K-BILD= King's Brief Interstitial Lung Disease Questionnaire; PD=premature discontinuation; PBMC=peripheral blood mononuclear cell; 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 during Screening may be repeated 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. 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 return for a clinic visit and undergo the Week 52 assessments. Subjects not entering the 52-week open-label extension trial will return to the clinic 4 weeks after the last dose of trial drug for a Safety Follow-up Visit.

Section 2.1 Schedule of Assessments (continued)

6. 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.
7. Baseline lung HRCT will be performed only if no lung HRCT is available within the last 6 months and can be performed any time between Screening and Day 1. Results are required to be sent for central review.
8. Histopathology samples used towards IPF diagnosis (if required) will be submitted for central review.
9. Subjects will be randomized in a 1:1:1 ratio to receive HZN-825 300 mg QD, HZN-825 300 mg BID or placebo.
10. For subjects who are entering the open-label extension.
11. The lung HRCT scan will be performed for all subjects within ±2 weeks of the Week 52/PD Visit.
12. If SARS-CoV-2 exposure is of clinical concern for any subject, consider using a DLCO up to 6 months before the Screening Visit.
13. 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).
14. A complete physical examination will be performed, including, but not limited to, cardiac, pulmonary and neurologic assessments.
15. Vital signs (blood pressure, heart rate, respiratory rate, temperature, pulse oximetry) will be measured at each clinic visit.
16. Additional electrocardiograms or echocardiograms will be conducted, if clinically indicated. An echocardiogram that has been performed within the prior 3 months can serve as the Baseline echocardiogram if the subject has been clinically stable.
17. Chemistry includes total protein, albumin, sodium, phosphate, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase, uric acid, lactate dehydrogenase; liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, total bile acid, total bilirubin and conjugated and unconjugated bilirubin, if applicable). Hematology includes hemoglobin, hematocrit, red blood cell count (with morphology if blood cell count is abnormal), white blood cell count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes) and platelet count. Samples collected at the Day 1 Visit should be collected before the morning dose of trial drug is administered in the clinic. For subjects taking warfarin, physicians should monitor their international normalized ratio, as needed.
18. Includes fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and fasting triglycerides. Samples collected at the Day 1 Visit should be collected before the morning dose of trial drug is administered in the clinic.
19. 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.
20. Includes recording of herb/supplement use. See Table 9.1 for restrictions regarding medications.
21. Includes recording of herb/supplement use. See Table 9.1 for restrictions regarding medications.
22. 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 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, a sample will be collected anytime during the Week 52 Visit. Record date/time of all samples.
23. 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 disease for the current trial.
24. 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.
25. 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.

to Baseline to serve as the Baseline echocardiogram if the subject has been clinically stable; remove the specification that the 6MWT will be performed at selected sites, as it will be performed at all sites; clarify the assessments to be included as part of the examination

Section 6 Investigators and Trial Administrative Structure **Table 6.1 → Table of Non-Sponsor Trial Responsibilities¶** **Trial Responsibility** / **Person/Organization** Contract research organization (project management and monitoring) / PPD Biotech, 929 North Front Street, Wilmington, NC 28401 Central safety laboratory / PPD Global Central Labs, LLC, 2 Tesseneer Drive, Highland Heights, KY 41076	**Section 6 Investigators and Trial Administrative Structure** **Table 6.1 Table of Non-Sponsor Trial Responsibilities** **Trial Responsibility** / **Organization** Contract research organization / PPD Biotech, 929 North Front Street, Wilmington, NC 28401 Central safety laboratory / PPD Laboratories – North, South and Latin America, 2 Tesseneer Drive, Highland Heights, KY 41076; PPD Laboratories – Europe, Middle East and Africa, Clusterpark, Kleine Kloosterstraat 19, 1932 Zaventem, Belgium; PPD Laboratories – Asia Pacific, 61, Science Park Road, #02-11/14, The Galen, Singapore Science Park II, Singapore 117525	*To provide regional addresses for the central safety laboratory*

Section 7.3 Rational for Dose Selection The dose regimens to be evaluated in this trial are 300 mg QD and 300 mg BID with food using HZN-825 tablets manufactured by [redacted]. These regimens are selected based on a comprehensive review of preclinical data assessing in vitro $LPAR_1$ inhibitory activity, information from rodent fibrosis models, Phase 1 PK data and information from a Phase 2a trial in SSc subjects. The completed Phase 2a trial in diffuse cutaneous SSc supports the safety and potential efficacy of 300 mg BID for up to 24 weeks of treatment. The exposures and safety profiles of HZN-825 in this trial were similar to those previously observed in healthy subjects, and positive changes in mRSS, HAQ-DI and $LPAR_1$ pathway genes were detected. The observed mean steady-state trough concentration ([redacted]) in the Phase 2a trial is thus considered a relevant target exposure of HZN-825 for IPF, as by blocking $LPAR_1$ signaling, HZN-825 has the potential to specifically and efficaciously resolve the underlying pathologies of IPF, thereby reducing the severity and progression of the disease. Preclinical data also support the HZN-825 exposures targeted for this trial. The minimum total C_{trough} in humans needed for inhibition of $LPAR_1$ activity was between 25.3 and 1536 ng/mL based on in vitro potency evaluations. The half-maximal inhibitory concentration (IC_{50}) of HZN-825 against $LPAR_1$ activity ranged from 1.1 to 66.8 ng/mL without presence of albumin, corresponding to 25.3 to 1536 ng/mL after adjusting for the 23-fold shift in IC_{50} in the presence of 3.5% albumin (in the range of human plasma albumin level of 3.5 to 4.5 g/dL [Human Albumin 2009]. In a rat deoxycorticosterone acetate (DOCA) salt model, HZN-825 reduced cardiac hypertrophy, hydroxyproline levels and kidney damage at 10 mg/kg BID, with a steady-state area under the concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) of 12000 ng*h/mL. Based on preliminary PK results from Trial HZNP-HZN-825-101, 300 mg BID dosing with food using HZN-825 Aptuit tablets is expected to achieve similar steady-state C_{trough} as observed in the Phase 2a trial in subjects with SSc and is selected as the higher dose in this trial. Additionally, there was less than dose-proportional	**Section 7.3 Rational for Dose Selection** The dose regimens to be evaluated in this trial are 300 mg QD and 300 mg BID with a meal using HZN-825 tablets manufactured by [redacted]. These regimens are selected based on a comprehensive review of preclinical data assessing in vitro $LPAR_1$ inhibitory activity, information from rodent fibrosis models, Phase 1 PK data and information from a Phase 2a trial in subjects with diffuse cutaneous SSc. The completed Phase 2a trial in diffuse cutaneous SSc supports the safety and potential efficacy of 300 mg BID for up to 24 weeks of treatment. The exposures and safety profiles of HZN-825 in this trial were similar to those previously observed in healthy subjects, and positive changes in mRSS, HAQ-DI and $LPAR_1$ pathway genes were detected. The observed mean steady-state trough concentration ([redacted]) in the Phase 2a trial is thus considered a relevant target exposure of HZN-825 for IPF, as by blocking $LPAR_1$ signaling, HZN-825 has the potential to specifically and efficaciously resolve the underlying pathologies of IPF, thereby reducing the severity and progression of the disease. Preclinical data also support the HZN-825 exposures targeted for this trial. The minimum total C_{trough} in humans needed for inhibition of $LPAR_1$ activity was between 25.3 and 1536 ng/mL based on in vitro potency evaluations. The half-maximal inhibitory concentration (IC_{50}) of HZN-825 against $LPAR_1$ activity ranged from 1.1 to 66.8 ng/mL without presence of albumin, corresponding to 25.3 to 1536 ng/mL after adjusting for the 23-fold shift in IC_{50} in the presence of 3.5% albumin (in the range of human plasma albumin level of 3.5 to 4.5 g/dL [Human Albumin 2009]. In a rat deoxycorticosterone acetate (DOCA) salt model, HZN-825 reduced cardiac hypertrophy, hydroxyproline levels and kidney damage at 10 mg/kg BID, with a steady-state area under the concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) of 12000 ng*h/mL. Based on preliminary PK results from Trial HZNP-HZN-825-101, 300 mg BID dosing with a meal using HZN-825 Aptuit tablets is expected to achieve similar steady-state C_{trough} as observed in the Phase 2a trial in subjects with SSc and is selected as the higher dose	*"With food" could be interpreted as dosing with a snack, which is not sufficient for targeted drug exposure*

increase in systemic exposures of HZN-825 from 150 mg to 300 mg (about 30% and 40% increase in C_{max} and area under the concentration-time curve [AUC], respectively) and no exposure increase from 300 mg to 450 mg with Aptuit tablets; also, food intake increased HZN-825 exposures. Therefore, a second, less-frequent dose regimen, 300 mg QD with food, is selected to provide a broad range of HZN-825 exposures (2-fold different for AUC and ~6-fold different for steady-state C_{trough}) for evaluation in this trial, a dose that is still expected to achieve pharmacologically active steady-state C_{trough} above the concentrations needed for in vitro inhibition of $LPAR_1$ activity. Additionally, after adjusting for plasma protein binding of HZN-825 between humans and rats (99.97% and 99.92%, respectively), both 300 mg QD and 300 mg BID are also expected to achieve AUC_{0-12h} above the AUC_{0-12h} that showed efficacy in the rat DOCA model. In summary, the plasma exposures associated with both HZN-825 300 mg QD and 300 mg BID are anticipated to be well tolerated and have clinical efficacy. The range of exposures achieved with these dose regimens will support efficient dose-range exploration and allow exposure-response evaluation of HZN-825 in subjects with IPF	in this trial. Additionally, there was less than dose-proportional increase in systemic exposures of HZN-825 from 150 mg to 300 mg (about 30% and 40% increase in C_{max} and area under the concentration-time curve [AUC], respectively) and no exposure increase from 300 mg to 450 mg with Aptuit tablets; also, food intake increased HZN-825 exposures. Therefore, a second, less-frequent dose regimen, 300 mg QD with a meal, is selected to provide a broad range of HZN-825 exposures (2-fold different for AUC and ~6-fold different for steady-state C_{trough}) for evaluation in this trial, a dose that is still expected to achieve pharmacologically active steady-state C_{trough} above the concentrations needed for in vitro inhibition of $LPAR_1$ activity. Additionally, after adjusting for plasma protein binding of HZN-825 between humans and rats (99.97% and 99.92%, respectively), both 300 mg QD and 300 mg BID are also expected to achieve AUC_{0-12h} above the AUC_{0-12h} that showed efficacy in the rat DOCA model. In summary, the plasma exposures associated with both HZN-825 300 mg QD and 300 mg BID are anticipated to be well tolerated and have clinical efficacy. The range of exposures achieved with these dose regimens will support efficient dose-range exploration and allow exposure-response evaluation of HZN-825 in subjects with IPF.	
Not applicable (section added to v2.0 of the protocol)	**Section 9.1.1 Adjudication Committee** Cases of respiratory hospitalizations and acute exacerbations will each be reviewed by an independent adjudication committee in a blinded manner before database lock. Details outlining the responsibilities of the adjudication committee and the parameters related to these events of interest will be included in the adjudication committee charter.	*To specify that an independent adjudication committee will review cases of respiratory hospitalizations and acute exacerbations*

Section 9.3.3 Removal of Subjects from Treatment or the Trial All subjects are free to withdraw from trial participation at any time, for any reason and without prejudice to their further medical care. In addition, the Investigator may terminate a subject from treatment at any time, if further participation in the trial is not in the best interest of the subject.	**Section 9.3.3 Removal of Subjects from Treatment or the Trial** All subjects are free to withdraw from trial participation at any time, for any reason and without prejudice to their further medical care. In addition, the Investigator may terminate a subject from treatment at any time, if further treatment in the trial is not in the best interest of the subject. 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.	*To minimize the amount of missing data, emphasizing that subjects who prematurely discontinue trial drug will be asked to remain in the trial, participating in the scheduled trial visits through Week 52*
Not applicable (section added to v2.0 of the protocol)	**Section 9.3.4 Discontinuation of a Treatment Group or the Trial** The following events, if applicable, may cause premature termination of the clinical trial or trial arms: unjustifiable risk and/or toxicity in risk-benefit analysis (decision taken by Sponsor or representative), e.g., when adverse events occur, unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile (substantial changes in risk-benefit considerations), and, therefore, medical and/or ethical reasons affect the continued performance of the trial; new scientific evidence becomes available during the trial that could affect the subject's safety (benefit-risk analysis no longer positive), e.g., new insights from other clinical trials; request of the Sponsor with or without recommendation from a data safety monitoring board, or of a regulatory agency, e.g., as a consequence of inspection; favorable opinion withdrawn by the ethics commission; in case of difficulties in the recruitment of the planned number of subjects in the indicated time (insufficient recruitment rate); and withdrawal of the license to manufacture (and/or of the permission to import).	*To add reasons that a treatment group or the trial may be discontinued*

Section 9.3.4.3 Screen Failures Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria will be considered screen failures. An abnormal test during Screening may be repeated during the Screening Period. Screen failures may be allowed to rescreen for the trial if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that the subject can satisfy all of the eligibility criteria.	**Section 9.3.5.3 Screen Failures** Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria will be considered screen failures. An abnormal test during Screening may be repeated once during the Screening Period. Screen failures may be allowed to rescreen for the trial if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that the subject can satisfy all of the eligibility criteria.	*To clarify that an abnormal test during Screening may be repeated once during the Screening Period*
Section 9.4.6 Trial Drug Administration and Timing of Dose for Each Subject Subjects will take 2 tablets of trial drug (HZN-825 150 mg and/or placebo) orally in the morning and evening with food. In the event a subject misses a dose, the dose should be taken along with the next planned dose (evening or morning) with food.	**Section 9.4.6 Trial Drug Administration and Timing of Dose for Each Subject** Subjects will take 2 tablets of trial drug (HZN-825 150 mg and/or placebo) orally in the morning and evening with a meal. In the event a subject misses a dose, the dose should be taken along with the next planned dose (evening or morning) with a meal.	*"With food" could be interpreted as dosing with a snack, which is not sufficient for targeted drug exposure*
Section 9.4.6.1.1 Orthostatic Hypotension Orthostatic hypotension is considered the AESI for this trial. Trial drug should be temporarily discontinued in the case of trial drug-related, newly developed and clinically significant orthostatic hypotension associated with clinical symptoms requiring medical intervention. Trial drug may be restarted at the discretion of the Investigator after the clinical symptoms have resolved.	**Section 9.4.6.1.1 Orthostatic Hypotension** Orthostatic hypotension is considered the AESI for this trial. Trial drug should be temporarily discontinued in the case of trial drug-related, newly developed and clinically significant orthostatic hypotension associated with clinical symptoms requiring medical intervention. Trial drug may be restarted at the discretion of the Investigator after the clinical symptoms have resolved and following consultation with the Sponsor trial medical monitor. Subjects should have normal blood pressure and heart rate with absence of symptoms related to orthostatic hypotension for at least 5 days prior to restarting.	*To provide guidance regarding restarting trial drug after a subject experiences clinically significant orthostatic hypotension*

Section 9.4.8 Blinding and Unblinding An IDMC will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when [redacted] The IDMC charter will include processes to unblind select Horizon personnel to assess unforeseen issues that may affect dose selection; otherwise, unblinded information will be restricted to IDMC members who are not involved in other aspects of the trial.	**Section 9.4.8 Blinding and Unblinding** An IDMC will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when [redacted] The IDMC charter will include processes to unblind select Horizon personnel to assess unforeseen issues that may affect dose selection; otherwise, unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management.	*To clarify that unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management unless other select Horizon personnel need to be unblinded*

Section 9.4.9 Concomitant Therapy and Restricted Medications

Other causes for FVC decline (i.e., respiratory tract infection) should be excluded. Repeat FVC/spirometry should be performed and confirmed prior to initiation of rescue medication.

Table 9.1 → Restricted Medications

Medication	Restricted Time Period
Prednisone at steady dose >10 mg/day or equivalent or cyclosporine A	4 weeks prior to Screening through trial completion Topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed during the trial. Short bursts for acute illnesses (asthma, allergic reaction) are permitted.
Other immunosuppressant agents	Treatment with any other immunosuppressant during the Screening Period through the end of trial participation will require consultation and approval by the trial Medical Monitor.
Commercially approved agent for interstitial lung disease or an investigational agent for any condition	90 days or 5 half-lives, whichever is longer, prior to Screening through trial completion
Drug/alcohol abuse	History of abuse within the past 2 years or abuse during trial
Rifampin	2 weeks prior to dosing through trial completion

AUC=area under the concentration-time curve; CYP=cytochrome P450; INR=international normalized ratio
For subjects taking warfarin, physicians should monitor their INR, as needed. HZN-825 is a weak inhibitor of CYP2C9, increasing S-warfarin AUC by 23% and R-warfarin AUC by 13% in healthy subjects, with minimal impact on INR (the mean increase in INR at 24 hours post warfarin administration from Baseline was 14.2% without HZN-825 and 16.8% with HZN-825 treatment).

Section 9.4.9 Concomitant Therapy and Restricted Medications

Other causes for FVC decline (i.e., respiratory tract infection) should be excluded. Repeat FVC/spirometry should be performed and confirmed prior to initiation of rescue medication if, to the Investigator's clinical judgment, well-founded doubts in the test's quality and the subject's good condition justify the associated delay in subject care, and the increase in risk for the subject.

Table 9.1 → Restricted Medications

Medication	Restricted Time Period
Prednisone at steady dose >10 mg/day or equivalent or cyclosporine A	4 weeks prior to Screening through trial completion Topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed during the trial. Short bursts for acute illnesses (asthma, allergic reaction) are permitted.
Other immunosuppressant agents	Treatment with any other immunosuppressant during the Screening Period through the end of trial participation will require consultation and approval by the trial Medical Monitor.
Commercially approved agent for interstitial lung disease or an investigational agent for any condition	90 days or 5 half-lives, whichever is longer, prior to Screening through trial completion
Drug/alcohol abuse	History of abuse within the past 2 years or abuse during trial
Rifampin[1]	2 weeks prior to dosing through trial completion
OATP inhibitors: clarithromycin, erythromycin and gemfibrozil. P-gp inhibitors: amiodarone, carvedilol, dronedarone, itraconazole, propafenone, quinidine, ranolazine and verapamil. BCRP inhibitor: eltrombopag	3 days prior to dosing through trial completion

AUC=area under the concentration-time curve; BCRP=breast cancer resistance protein; CYP=cytochrome P450; INR=international normalized ratio; OATP=organic anion transporter polypeptide; P-gp=P-glycoprotein
For subjects taking warfarin, physicians should monitor their INR, as needed. HZN-825 is a weak inhibitor of CYP2C9, increasing S-warfarin AUC by 23% and R-warfarin AUC by 13% in healthy subjects, with minimal impact on INR (the mean increase in INR at 24 hours post warfarin administration from Baseline was 14.2% without HZN-825 and 16.8% with HZN-825 treatment).

1. Rifampicin is a CYP enzyme inducer and an OATP inhibitor.

To add OATP inhibitors, P-gp inhibitors and a BRCP inhibitor as restricted medications

<table>
<tr>
<td>

Section 9.4.9 Concomitant Therapy and Restricted Medications

Table 9.2 Medications Allowed After Week 28 Due to Clinically Significant Deterioration

Medication	Screening Period	Treatment and Post-treatment Follow-up Periods
Non-steroidal medication		
Nintedanib	Not permitted	Not permitted except for deterioration [1]
Pirfenidone	Not permitted	Not permitted except for deterioration [1]
Mycophenolate mofetil/CellCept ≤3 g/day, Myfortic ≤2.14 g/day	Not permitted	Not permitted except for deterioration [1]
Cyclophosphamide	Not permitted within 4 weeks of Screening	Not permitted except for deterioration [1]
Steroids		
Prednisone >10 mg/day	Not permitted 4 weeks prior to the Day 1 Visit	Not permitted except for deterioration [1]

DLCO=diffusing capacity of the lungs for carbon monoxide; FVC=forced vital capacity

1. Initiation/change in dose permitted after the Week 28 Visit in case of clinically significant deterioration, defined as:
   - An absolute decline since Baseline in FVC % predicted ≥10% or an absolute decline since Baseline in FVC % predicted ≥5 to 9% with associated decline in DLCO ≥15% from Baseline, or
   - Clinically significant deterioration in other organ systems, per Investigator assessment.

   Other causes for FVC decline (i.e., respiratory tract infection) should be excluded.

</td>
<td>

Section 9.4.9 Concomitant Therapy and Restricted Medications

Table 9.2 Rescue Medications Allowed After Week 28 Due to Clinically Significant Deterioration

Medication	Screening Period	Treatment and Post-treatment Follow-up Periods
Non-steroidal medication		
Nintedanib	Not permitted	Not permitted except for deterioration [1]
Pirfenidone	Not permitted	Not permitted except for deterioration [1]
Mycophenolate mofetil/CellCept ≤3 g/day, Myfortic ≤2.14 g/day	Not permitted	Not permitted except for deterioration [1]
Cyclophosphamide	Not permitted for 4 weeks prior to Screening and throughout Screening	Not permitted except for deterioration [1]
Steroids		
Prednisone >10 mg/day	Not permitted for 4 weeks prior to Screening and throughout Screening	Not permitted except for deterioration [1]

DLCO=diffusing capacity of the lungs for carbon monoxide; FVC=forced vital capacity

1. Initiation/change in dose permitted after the Week 28 Visit in case of clinically significant deterioration, defined as:
   - An absolute decline since Baseline in FVC % predicted ≥10% or an absolute decline since Baseline in FVC % predicted ≥5 to 9% with associated decline in DLCO ≥15% since Baseline, or
   - Clinically significant deterioration in other organ systems, per Investigator assessment.

   Other causes for FVC decline (i.e., respiratory tract infection) should be excluded. Repeat FVC/spirometry should be performed and confirmed prior to initiation of rescue medication if, to the Investigator's clinical judgment, well-founded doubts in the test's quality and the subject's good condition justify the associated delay in subject care, and the increase in risk for the subject.

</td>
<td>

To indicate Investigator discretion in repeat of spirometry prior to rescue medication and clarify that cyclophos-phamide and prednisone >10 mg/day are not permitted for 4 weeks prior to Screening and throughout Screening

</td>
</tr>
<tr>
<td>

Section 9.5.4.1.5 Reporting and Documenting Serious Adverse Events

1. Report the SAE to the Sponsor by entering the information into the eCRF within 24 hours after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form within 24 hours after becoming aware that a subject has experienced an SAE (see Section 17.1 for contact information).

</td>
<td>

Section 9.5.5.1.5 Reporting and Documenting Serious Adverse Events

1. Report the SAE to the Sponsor by entering the information into the eCRF **immediately, without undue delay but not later than 24 hours** after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form **immediately, without undue delay but not later than 24 hours** after becoming aware that a subject has experienced an SAE (see Section 17.1 for contact information).

</td>
<td>

To clarify SAE reporting requirements

</td>
</tr>
</table>

Section 9.5.4.1.5.1 Monitoring of Serious Adverse Events Anticipated in the Trial Population SAEs are anticipated to occur in the trial population independent of the subject's exposure to trial drug. These anticipated SAEs are provided in Section 17.7 (Serious Adverse Events Anticipated in the Trial Population) for reference. The list does NOT change the Investigator's reporting obligations or prevent the need to report an AE meeting the definition of an SAE, as detailed above. The purpose of this list is to alert the Investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities if they are on this list. The Sponsor will monitor these events throughout the course of the trial for any change in frequency.	**Section 9.5.5.1.5.1 Monitoring of Serious Adverse Events Anticipated in the Trial Population** SAEs are anticipated to occur in the trial population independent of the subject's exposure to trial drug. These anticipated SAEs are provided in Section 17.8 (Serious Adverse Events Anticipated in the Trial Population) for reference. The list does NOT change the Investigator's reporting obligations or prevent the need to report an AE meeting the definition of an SAE, as detailed above. The purpose of this list is to alert the Investigator that some events reported as SAEs that are anticipated to occur in the trial population due to underlying disease, may not require expedited reporting to the regulatory authorities in every country/region. The Sponsor will monitor these events throughout the course of the trial for any change in frequency.	*To clarify local reporting obligations for SAEs*
Section 9.5.4.1.10 Development Safety Update Reports The Sponsor will prepare and submit annual safety reports to the US FDA.	**Section 9.5.5.1.10 Development Safety Update Reports** The Sponsor will prepare and submit annual safety reports to the US FDA. Drug safety update reports will also be submitted to countries and territories as required.	*To include a statement that development safety update reports will be submitted to countries and territories as required*

Section 9.5.4.2 Pregnancy Reporting
Pregnancy testing will be performed for women of childbearing potential. Serum pregnancy tests will be analyzed at a central trial laboratory and the urine pregnancy tests will be performed locally.
If a female subject becomes pregnant during the Double-blind Treatment Period, she should immediately notify the Investigator and trial drug dosing should be permanently discontinued but the subject will be asked to continue in the trial for evaluations.
Pregnancy occurring in the partner of a male subject participating in the trial should be reported to the Investigator and the Sponsor immediately upon awareness of pregnancy. Monitoring of the subject's partner should continue until conclusion of the pregnancy.
Subjects should be instructed to continue contraception for 4 weeks after their last dose of trial drug. Pregnancies occurring up to 4 weeks after the last dose of trial drug must also be reported to the Investigator.
The Investigator should report pregnancies to the Sponsor within 24 hours by submitting the completed pregnancy report form within 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see Section 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy. If pregnancy continues and the subject signs the pregnancy consent form, monitoring should also continue to the conclusion of the pregnancy.
	Section 9.5.5.2 Pregnancy Reporting
	Pregnancy testing will be performed for WOCBP. Serum pregnancy tests will be analyzed at a central trial laboratory and the urine pregnancy tests will be performed locally. In addition, at-home pregnancy tests will be completed by WOCBP at Weeks 8, 12, 20, 24, 32, 36, 44 and 48, and results will be reported to the site.
	If a female subject becomes pregnant during the Double-blind Treatment Period, she should immediately notify the Investigator and trial drug dosing should be permanently discontinued but the subject will be asked to continue in the trial for evaluations.
	Pregnancy occurring in the partner of a male subject participating in the trial should be reported to the Investigator and the Sponsor immediately upon awareness of pregnancy. Monitoring of the subject's partner should continue until conclusion of the pregnancy.
	Subjects should be instructed to continue contraception for 4 weeks after their last dose of trial drug. Pregnancies occurring up to 4 weeks after the last dose of trial drug must also be reported to the Investigator.
	Some examples of highly effective contraceptive methods that have a failure rate of <1% per year when used consistently and correctly are:
	• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
	  ○ Oral
	  ○ Intravaginal
	  ○ Transdermal
	• Progestogen-only hormonal contraception associated with inhibition of ovulation
	  ○ Oral
	  ○ Injectable
	  ○ Implantable
	• Intrauterine device (IUD)
	• Intrauterine hormone-releasing system (IUS)
	• Bilateral tubal ligation
		To change pregnancy testing to every 4 weeks and add specifics regarding pregnancy outcome follow-up and examples of highly effective contraceptive methods

	• Vasectomized partner • Sexual abstinence from heterosexual intercourse There are no expected drug interactions between HZN-825 and hormonal contraceptives. The Investigator should report pregnancies to the Sponsor within 24 hours by submitting the completed pregnancy report form within 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see Section 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy. If pregnancy continues and the subject signs the pregnancy consent form, the subject will be contacted 2 weeks after her calculated delivery time to provide information about the outcome of the pregnancy and the well-being of the child. A final contact will be made 8 weeks after delivery, when the subject will again be asked about the well-being of the child.	
Section 9.5.4.6 Physical Examination A physical examination will be performed per the Schedule of Assessments (Section 2.1).	**Section 9.5.5.6 Physical Examination** A complete physical examination, including but not limited to, cardiac, pulmonary and neurologic assessments, will be performed per the Schedule of Assessments (Section 2.1).	*To clarify the assessments to be included as part of the physical examination*

Section 9.5.4.9 Laboratory Tests for Evaluation A central trial laboratory will be used for all protocol-specified laboratory evaluations, with the exception of urine pregnancy tests that will be performed locally at each site. Chemistry parameters to be evaluated include total protein, albumin, sodium, phosphate, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase, uric acid, glucose (fasting), lactate dehydrogenase; liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, total bile acid, total bilirubin, conjugated and unconjugated bilirubin, if applicable); lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting triglycerides). Hematology parameters to be evaluated include hemoglobin, hematocrit, red blood cell count (with morphology if blood cell count is abnormal), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), reticulocyte count, white blood cell count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes) and platelet count.	**Section 9.5.5.9 Laboratory Tests for Evaluation** A central trial laboratory will be used for all protocol-specified laboratory evaluations, with the exception of urine pregnancy tests that will be performed locally at each site or at-home, as applicable, in order to maintain monthly pregnancy testing. Chemistry parameters to be evaluated include total protein, albumin, sodium, phosphate, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase, uric acid, lactate dehydrogenase; liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, total bile acid, total bilirubin, conjugated and unconjugated bilirubin, if applicable). Fasting glucose and fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides) will also be evaluated (see Section 2.1). Hematology parameters to be evaluated include hemoglobin, hematocrit, red blood cell count (with morphology if blood cell count is abnormal), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW), reticulocyte count, white blood cell count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes) and platelet count.	*To change pregnancy testing to every 4 weeks and fasting glucose to be analyzed at the same time points as lipid profile*
Section 9.5.6 Trial Procedures Trial procedures and timing are detailed in the Schedule of Assessments (Section 2.1) and operations manual.	**Section 9.5.7 Trial Procedures** Trial procedures and timing are detailed in the Schedule of Assessments (Section 2.1). The end of the trial is defined as the date of the last visit of the last subject undergoing the trial.	*To define end of trial*
Section 9.5.8 Long-term Survival Follow-up Following the end of the trial or after premature withdrawal, the Investigator or designee may follow the long-term health of subjects for up to 5 years via inspection of hospital records or publicly available sources.	Section deleted from v2.0 of the protocol	*To remove long-term survival follow-up*

Section 9.6.1.6 Pharmacodynamic Endpoint 1. Pharmacodynamic effects of HZN-825 on biomarkers	Section deleted from v2.0 of the protocol**.**	*To correct an error in the original protocol because evaluation of pharmaco-dynamics is exploratory and not an objective of the trial*
Section 9.6.4 Secondary Efficacy Endpoint Analyses Changes from Baseline in 6MWT, K-BILD, L-IPF and LCQ scores will be analyzed analogously to the primary efficacy endpoints. The rate of hospitalization due to respiratory distress will be analyzed analogously to the PFS endpoint described above.	**Section 9.6.4 Secondary Efficacy Endpoint Analyses** Changes from Baseline in 6MWT, K-BILD, L-IPF and LCQ scores will be analyzed analogously to the primary efficacy endpoints. Survival analysis will be used for the time-to-event endpoints, including time to the first onset of the composite endpoint and the time to the first hospitalization due to respiratory distress. A Cox proportional hazard model stratified like the previous logistic model with baseline FVC % predicted and treatment group will provide hazard ratio, its 95% CI and p-value to compare each HZN-825 group with the placebo group.	*To update the description of the secondary efficacy endpoint analyses*
[redacted]		
Not applicable (section added to v2.0 of the protocol)	**Section 17.2 Hospitalization Due to Respiratory Distress** See Section 17.2.	*To add an appendix pertaining to*

		hospitaliza-tion due to respiratory distress
Section 17.2 IPF-related Acute Exacerbation The conceptual framework for evaluation of acute respiratory deterioration in IPF, as defined by Collard et al., 2016, is shown in Figure 17.1. Acute respiratory deterioration of IPF (defined as "typically, 1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural effusion) or parenchymal. Parenchymal causes that demonstrate new bilateral ground-glass opacification/consolidation on computed tomography that is not fully explained by cardiac failure or fluid overload are categorized as acute exacerbations of IPF, regardless of the presence or absence of a known trigger (e.g., infection). Acute exacerbations are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found.	**Section 17.3 IPF-related Acute Exacerbation** Clinical information for potential IPF-related acute exacerbations will be collected on a dedicated questionnaire. In addition, all relevant clinical data (summary on clinical course, signs and symptoms; laboratory, lung function and imaging results; and treatment provided) relating to the exacerbation will be collected and provided to an independent adjudication committee for review. The conceptual framework for evaluation of acute respiratory deterioration in IPF, as defined by Collard et al., 2016, is shown in Figure 17.2. Acute respiratory deterioration of IPF (defined as "typically, 1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural effusion) or parenchymal. Parenchymal causes that demonstrate new bilateral ground-glass opacification/consolidation on computed tomography that is not fully explained by cardiac failure or fluid overload are categorized as acute exacerbations of IPF, regardless of the presence or absence of a known trigger (e.g., infection). Acute exacerbations are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found. For additional details, refer to the adjudication committee charter.	*To specify that clinical information for potential IPF-related acute exacer-bations will be collected on a dedicated questionnaire and that all relevant data will be provided to an independent adjudication committee for review*