CLINICAL TRIAL PROTOCOL

FOR FIPAXALPARANT (HZN-825)

Protocol Number: HZNP-HZN-825-302
IND: 112818
EU CT Number: 2023-509783-23-00

A Multicenter, Open-label Extension Trial to Evaluate the Efficacy, Safety and Tolerability of HZN-825 in Patients with Diffuse Cutaneous Systemic Sclerosis

Date: 14 October 2024

Version 3.0

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 Multicenter, Open-label Extension Trial to Evaluate the Efficacy, Safety and Tolerability of HZN-825 in Patients with Diffuse Cutaneous Systemic Sclerosis
Protocol Number:	HZNP-HZN-825-302
Version:	3.0
Investigational Product:	Fipaxalparant (HZN-825)
Indication:	Systemic sclerosis
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] MD Medical Director, Clinical Development Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015
Approval Date:	14 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.

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

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-HZN-825-302

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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 TABLE OF CHANGES
Protocol Version 2.0, Amendment 1 (19 October 2022) to Protocol Version 3.0, Amendment 2 (14 October 2024)

Text Version 2.0 19 October 2022	Amended Text Version 3.0, Amendment 2 14 October 2024	Reason for Change
Global HZN-825	**Global** fipaxalparant (HZN-825)	*To incorporate non-proprietary name throughout document*
Global Physician Global Assessment (MDGA)	**Global** Clinician Global Assessment (CGA)	*To align with industry standard language*
Cover Page EudraCT Number: 2021-006271-42	**Cover Page** EU CT Number: 2023-509783-23-00	*To update in alignment with EU CT submission*
Cover Page and Title Page Horizon Therapeutics Ireland DAC	**Cover Page and Title Page** Horizon Therapeutics Ireland DAC (a wholly owned subsidiary of Amgen Inc.)	*To clarify new company structure*
Title Page **Sponsor's Responsible Medical Officer and Signatory:** [redacted], MD, MS Vice President, Clinical Development Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015	**Title Page** **Sponsor's Responsible Medical Officer:** [redacted], MD Medical Director, Clinical Development Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015	*To change the Sponsor's approver with shift to Amgen processes and update medical officer information*

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 Email: clinicalsafety@horizontherapeutics.com US Fax: 800-860-7836 Ex-US Fax: +1-224-855-5055	**Title Page** Email (worldwide): svc-ags-in-us@amgen.com US Fax: 1-888-814-8653 (toll free, within USA) Ex-US Fax: +44 (0)207-136-1046	*To update with new company structure*
Sponsor Signature Page	**Removed**	*To change the Sponsor's approver with shift to Amgen processes*
Synopsis – Objectives and Section 8 Trial Objectives and Section 9.6.1 Endpoints • HZN-825 Baseline, defined as the latest measurement prior to the first dose of HZN-825 in either Trial HZNP-HZN-825-301 or this extension trial. For subjects who received placebo in Trial HZNP-HZN-825-301, Trial Baseline will be the same as HZN-825 Baseline.	**Synopsis – Objectives and Section 8 Trial Objectives and Section 9.6.1 Endpoints** • Fipaxalparant (HZN-825) Baseline, defined as the latest measurement prior to the first dose of the trial drug in Trial HZNP-HZN-825-301.	*To improve clarity on baseline definitions*
Synopsis – Exploratory Objectives and Section 8.2 Exploratory Objectives • Change from both Baselines in Health Assessment Questionnaire - Disability Index (HAQ-DI); Physician Global Assessment (MDGA); Patient Global Assessment (PTGA); the Physical Effects and Physical Limitations subscales of the scleroderma skin patient-reported outcome (SSPRO-18); the modified Rodnan skin score (mRSS); American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from each	**Synopsis – Exploratory Objectives and Section 8.2 Exploratory Objectives** • Change from both Baselines in the modified Rodnan skin score (mRSS), the Revised Composite Response Index in Systemic Sclerosis (Revised CRISS [CRISS 25]), Health Assessment Questionnaire - Disability Index (HAQ-DI); Clinician Global Assessment (CGA); Patient Global Assessment (PTGA); the Physical Effects and Physical Limitations subscales of the scleroderma skin patient-reported outcome (SSPRO-18); proportion of subjects with clinically	*To align with updates in the HZN-825-301 study objectives with a goal of enhancing the ability to demonstrate overall improvement in the disease -*

Baseline in mRSS, HAQ-DI, PTGA, MDGA and FVC % predicted; ACR-CRISS-20, defined as improvement from both Baselines in ≥3 core set measures of ≥20% in mRSS, ≥20% in HAQ-DI, ≥20% in PTGA, ≥20% in MDGA and ≥5% in FVC % predicted; the SSPRO-18; the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0); Raynaud's phenomenon using the Raynaud's Assessment; the Scleroderma HAQ (SHAQ); Systemic Sclerosis Quality of Life Questionnaire (SScQoL); SF-12® Health Survey (SF-12); pain and pain component scale scores; fatigue based on the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F); lung fibrosis in subjects with suitable Baseline high-resolution computed tomography (HRCT); diffusing capacity of the lungs for carbon monoxide (DLCO); serum and plasma biomarkers associated with $LPAR_1$ pathway, inflammation and/or fibrosis; and [redacted] • The pharmacokinetics (PK) of HZN-825 and metabolite(s).	important change in the mRSS; American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from each Baseline in mRSS, HAQ-DI, PTGA, CGA and FVC % predicted; the SSPRO-18; the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0); Raynaud's phenomenon using the Raynaud's Assessment; the Scleroderma HAQ (SHAQ); Systemic Sclerosis Quality of Life Questionnaire (SScQoL); SF-12® Health Survey (SF-12); pain and pain component scale scores; fatigue based on the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F); lung fibrosis in subjects with suitable baseline high-resolution computed tomography (HRCT); diffusing capacity of the lungs for carbon monoxide (DLCO); serum and plasma biomarkers associated with $LPAR_1$ pathway, inflammation and/or fibrosis; and [redacted] • The pharmacokinetics (PK) of fipaxalparant (HZN-825).	*Improvement in mRSS score is associated with favorable outcomes including better survival in patients with dcSSc. Composite endpoint like CRISS 25 will help in global evaluation of likelihood of improvement.*
Synopsis – Trial Design and Section 9.1 Overall Trial Design and Plan Subjects entering this extension trial will complete the Week 52 Visit activities in HZNP-HZN-825-301 and will not complete the Safety Follow-up Visit 4 weeks after the last dose of trial drug in HZNP-HZN-825-301.	**Synopsis – Trial Design and Section 9.1 Overall Trial Design and Plan** Subjects entering this extension trial will complete the Week 52 Visit activities in HZNP-HZN-825-301 and will not complete the Safety Follow-up Visit 4 weeks after the last dose of trial drug in HZNP-HZN-825-301. All HZNP-HZN-825-301 Week 52 assessments should be performed before the first dose of the extension trial drug is administered.	*To ensure subjects complete the previous study in its entirety before starting the next treatment*

Synopsis – Trial Design Schematic and Figure 9.1 Schematic of Trial Design– Trial Baseline Column and Footnote Day 1 (Week 52 Visit of HZNP-HZN-825-301) BID=twice daily	**Synopsis – Trial Design Schematic and Figure 9.1 Schematic of Trial Design– Trial Baseline Column and Footnote** Day 1 (Week 52 Visit of HZNP-HZN-825-301)[1] BID=twice daily 1.All HZNP-HZN-825-301 Week 52 assessments should be performed before the first dose of the extension trial drug is administered.	*To ensure subjects complete the previous study in its entirety before starting the next treatment*
Synopsis – Criteria for Evaluation Blood samples for HZN-825 and metabolite(s) PK assessment, autoantibodies and biomarkers associated with the $LPAR_1$ pathway, inflammation and/or fibrosis will be collected.	**Synopsis – Criteria for Evaluation** Blood samples for fipaxalparant (HZN-825) PK assessment, autoantibodies and biomarkers associated with the $LPAR_1$ pathway, inflammation and/or fibrosis will be collected.	*To align with the HZN-825-301 study*
Synopsis – Statistical Analyses – Exploratory Efficacy Endpoints and Section 9.6.1.2 Exploratory Efficacy Endpoints 1.Change from both Baselines in HAQ-DI at Week 52. 2.Change from both Baselines in MDGA at Week 52. 3.Change from both Baselines in PTGA at Week 52. 4.Change from both Baselines in the Physical Effects subscale of the SSPRO-18 at Week 52. 5.Change from both Baselines in the Physical Limitations subscale of the SSPRO-18 at Week 52. 6.Proportion of subjects with an mRSS decrease of ≥5 points and 25% from both Baselines at Week 52. 7.Responder rate (defined as ACR-CRISS [predicted probability] of at least 0.6) at Week 52. 8.Proportion of subjects with an improvement in ≥3 of 5 core measures from both Baselines: ≥20% in mRSS, ≥20% in HAQ DI, ≥20% in PTGA, ≥20% in MDGA and ≥5% in FVC % predicted at Week 52 (ACR CRISS 20). 9.Change from both Baselines in the SSPRO-18 at Week 52. 10.Change from both Baselines in each scale of the UCLA SCTC GIT 2.0 and the total GIT score at Week 52.	**Synopsis – Statistical Analyses – Exploratory Efficacy Endpoints and Section 9.6.1.2 Exploratory Efficacy Endpoints** 1.Change from both Baselines in the mRSS at Week 52. 2.Proportion of subjects responding to treatment based on CRISS 25 at Week 52. 3.Change from both Baselines in HAQ-DI at Week 52. 4.Change from both Baselines in CGA at Week 52. 5.Change from both Baselines in PTGA at Week 52. 6.Change from both Baselines in the Physical Effects subscale of the SSPRO-18 at Week 52. 7.Change from both Baselines in the Physical Limitations subscale of the SSPRO-18 at Week 52. 8.Proportion of subjects with an mRSS decrease of ≥5 points and 25% from both Baselines at Week 52. 9.Responder rate (defined as ACR-CRISS [predicted probability] of at least 0.6) at Week 52. 10.Change from both Baselines in the SSPRO-18 at Week 52. 11.Change from both Baselines in each scale of the UCLA SCTC GIT 2.0 and the total GIT score at Week 52.	*To align with updates in the HZN-825-301 study endpoints with a goal of enhancing the ability to demonstrate overall improvement in the disease-Improvement in mRSS score is associated with favorable outcomes including better survival in patients with dcSSc. Composite endpoint like CRISS 25 will*

11.Change from both Baselines in Raynaud's phenomenon using the Raynaud's Assessment at Week 52. 12.Change from both Baselines in the SHAQ at Week 52. 13.Change from both Baselines in SScQoL scores at Week 52. 14.Change from both Baselines in SF-12 scores at Week 52. 15.Change from both Baselines in pain and pain component scale scores at Week 52. 16.Change from both Baselines in the FACIT-F score at Week 52. 17.Change from both Baselines in the mRSS at Week 52. 18.Change from both Baselines in lung fibrosis based on HRCT at Week 52. 19.Change from both Baselines in DLCO at Week 52. 20.Change from both Baselines in serum and plasma biomarkers associated with $LPAR_1$ pathway, inflammation and/or fibrosis at [redacted] 21.Change from both Baselines in [redacted]	12.Change from both Baselines in Raynaud's phenomenon using the Raynaud's Assessment at Week 52. 13.Change from both Baselines in the SHAQ at Week 52. 14.Change from both Baselines in SScQoL scores at Week 52. 15.Change from both Baselines in SF-12 scores at Week 52. 16.Change from both Baselines in pain and pain component scale scores at Week 52. 17.Change from both Baselines in the FACIT-F score at Week 52. 18.Change from both Baselines in lung fibrosis based on HRCT at Week 52. 19.Change from both Baselines in DLCO at Week 52. 20.Change from both Baselines in serum and plasma biomarkers associated with $LPAR_1$ pathway, inflammation and/or fibrosis at [redacted] 21.Change from both Baselines in [redacted]	*help in global evaluation of likelihood of improvement.*
Synopsis – Statistical Analyses – Safety and Tolerability Endpoints and Section 9.6.1.3 Safety and Tolerability Endpoints 3.Change from both Baselines in vital signs. 4.Change from both Baselines in 12-lead ECG measurements. 5.Change from both Baselines in clinical safety laboratory test results.	**Synopsis – Statistical Analyses – Safety and Tolerability Endpoints and Section 9.6.1.3 Safety and Tolerability Endpoints** 3.Vital signs. 4.12-lead ECGs. 5.Clinical safety laboratory evaluations.	*To align with the HZN-825-301 study*
Synopsis – Statistical Analyses – Pharmacokinetic Endpoint and Section 9.6.1.4 Pharmacokinetic Endpoint 1.Pre- and post-dose concentrations of HZN-825 and metabolite(s).	**Synopsis – Statistical Analyses – Pharmacokinetic Endpoint and Section 9.6.1.4 Pharmacokinetic Endpoint** 1.Pre- and post-dose concentrations of fipaxalparant (HZN-825).	*To align with the HZN-825-301 study*

Section 2.1 Schedule of Assessments – Safety Follow-up Column **Safety Follow-up Visit [1]**	**Section 2.1 Schedule of Assessments – Safety Follow-up Column** **Safety Follow-up Visit**	*To provide clarity that Safety Follow-up cannot be performed by home health visit*
List of Abbreviations	**List of Abbreviations** CGA Clinician Global Assessment CRISS 25 Composite Response Index in Systemic Sclerosis 25 DSUR Development Safety Update Report EDC electronic data capture EU European Union Revised CRISS Revised Composite Response Index in Systemic Sclerosis	*For defining new abbreviations used in body of document*
Section 6 Investigators and Trial Administrative Structure The Sponsor of this trial is Horizon Therapeutics Ireland DAC (Horizon).	**Section 6 Investigators and Trial Administrative Structure** The Sponsor of this trial is Horizon Therapeutics Ireland DAC (Horizon, a wholly owned subsidiary of Amgen Inc.).	*To clarify new company structure*
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 PK profiles across healthy subjects (including elderly healthy subjects) and subjects with diffuse cutaneous SSc.	**Section 7.1.3.4 Clinical Experience** Fipaxalparant (HZN-825) has been administered to 244 healthy subjects in 9 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 PK profiles across healthy subjects (including elderly healthy subjects) and subjects with diffuse cutaneous SSc.	*To update numbers based on most recently completed studies*

Section 7.1.3.4 Clinical Experience [redacted] that will continue to be monitored as an AE of special interest (AESI) (Section 9.5.3.1.1.4).	**Section 7.1.3.4 Clinical Experience** [redacted] that will continue to be monitored as an AE of special interest (AESI) (Section 9.5.3.1.1.4). Additionally, increases in [redacted] 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).	*To update in alignment with additional risks observed with use of investigational product*
Section 7.1.3.5 Benefit/Risk Assessment Based on the cumulative safety data available to date on HZN-825, [redacted], drug-drug interactions, embryo-fetal toxicity and liver toxicity are considered as important potential risks.	**Section 7.1.3.5 Benefit/Risk Assessment** Based on the cumulative safety data available to date on fipaxalparant (HZN-825), transaminase increase has been evaluated as an important identified risk and [redacted], drug-drug interactions, and embryo-fetal toxicity are considered as important potential risks.	*To update in alignment with additional risks observed with use of investigational product*
Section 7.3 Rationale for Dose Selection The dose regimen to be evaluated in this trial is 300 mg BID taken with a meal using HZN 825 tablets manufactured by [redacted].	**Section 7.3 Rationale for Dose Selection** The dose regimen to be evaluated in this trial is 300 mg BID taken with a meal using fipaxalparant (HZN-825) tablets manufactured by [redacted] and [redacted]	*To account for additional manufacturing site*
Section 9.3.3.1 Removal of Subjects from Treatment 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.	**Section 9.3.3.1 Removal of Subjects from Treatment** 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 (refer to Appendix 17.15). 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 remove option for continued dosage and promote subject safety*

Section 9.4.6.1.2 Drug-induced Liver Injury Refer to Section 9.3.3.1 for criteria regarding discontinuation of HZN-825 due to drug-induced liver injury.	**Section 9.4.6.1.2 Drug-induced Liver Injury** Elevated [redacted] have been evaluated to be an important identified risk with fipaxalparant (HZN-825). The events are mostly non-serious and reversible. Refer to Section 9.3.3.1 for criteria regarding trial drug discontinuation due to drug-induced liver injury.	*To update in alignment with additional risks observed with use of investigational product*
Section 9.4.9 Concomitant Therapy and Restricted Medications Caution should be observed when coadministering fipaxalparant (HZN-825) with strong inhibitors of [redacted].	**Section 9.4.9 Concomitant Therapy and Restricted Medications** Caution should be observed when coadministering fipaxalparant (HZN-825) with strong inhibitors of [redacted]. Fipaxalparant (HZN-825) is an in vitro inhibitor of OAT1 and OAT3 and may increase the systemic exposures of methotrexate.	*To advise caution on potential safety risks*
Section 9.5.1.2 Clinician Global Assessment 9.5.1.2 Physician Global Assessment The MDGA is an 11-point Likert scale ranging from 0 to 10 (0=excellent to 10=extremely poor) on which the physician rates the subject's overall health over the past week.	**Section 9.5.1.2 Clinician Global Assessment** 9.5.1.2 Clinician Global Assessment The CGA is also known as Physician Global Assessment (MDGA). The CGA is an 11-point Likert scale ranging from 0 to 10 (0=excellent to 10=extremely poor) on which the physician rates the subject's overall health over the past week.	*To align with industry-standard language*
Section 9.5.1.5 Revised Composite Response Index in Systemic Sclerosis (CRISS 25) **New section, subsequent sections re-numbered with this insertion**	**Section 9.5.1.5 Revised Composite Response Index in Systemic Sclerosis (CRISS 25)** The Revised CRISS (CRISS 25) is defined as improvement in at least 2 components: ≥5% increase for FVC % predicted and/or ≥25% decrease for mRSS, HAQ-DI, PTGA, CGA and worsening in no more than one component: ≥5% decrease percent predicted FVC and/or ≥25% increase for mRSS, HAQ-DI, PTGA, CGA, at 52 weeks. Revised CRISS (CRISS 25) is also a 2-step process. If the subject meets Step 1 (as defined in Section 9.5.1.4), they are considered not improved, given a percentage change of 0% for each core set item. In Step 2, the five core set measures are individually collected and scored.	*To define the CRISS 25 as has been added to study objectives*
Section 9.5.1.6 Plasma and Serum Biomarkers Blood samples will be collected prior to dosing on [redacted], [redacted] as well as at the [redacted] Visit for analysis	**Section 9.5.1.6 Plasma and Serum Biomarkers** Blood samples will be collected prior to dosing on [redacted], [redacted] as well as at the [redacted] Visit for analysis	*To correct the samples collected Week*

of plasma and serum biomarkers associated with the $LPAR_1$ pathway, inflammation or fibrosis.	of plasma and serum biomarkers associated with the $LPAR_1$ pathway, inflammation or fibrosis.	*42 to the correct Week 40*
Section 9.5.2 Pharmacokinetic Measurements Blood samples will be collected from all subjects to evaluate the PK of HZN-825 and metabolite(s) at each of the following visits: Day 1 (pre-dose), Week 4 (pre-dose and 2 to 4 hours post-dose) and Weeks 16, 28 and 40 (pre-dose only at these 3 visits).	**Section 9.5.2 Pharmacokinetic Measurements** Blood samples will be collected from all subjects to evaluate the PK of fipaxalparant (HZN-825) at each of the following visits: Day 1 (pre-dose), Week 4 (pre-dose and 2 to 4 hours post-dose) and Weeks 16, 28 and 40 (pre-dose only at these 3 visits).	*To align with the HZN-825-301 study*
Section 9.5.3.1.2 Documentation of Adverse Events If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by HZN 825, the Investigator will report this SAE using the procedures described in Section 9.5.3.1.5.	**Section 9.5.3.1.2 Documentation of Adverse Events** If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by fipaxalparant (HZN-825), the Investigator will report this SAE using the procedures described in Section 9.5.3.1.5. 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*
Section 9.5.3.1.4 Relationship or Causality to Fipaxalparant (HZN-825) The relationship of HZN-825 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.	**Section 9.5.3.1.4 Relationship or Causality to Fipaxalparant (HZN-825)** 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.	*To align with new sponsor standard safety reporting language*

	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 fipaxalparant (HZN-825) 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.	
Section 9.5.3.1.5 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). 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.	**Section 9.5.3.1.5 Reporting and Documenting Serious Adverse Events** 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 form **immediately and not later than 24 hours** after becoming aware that a subject has experienced an SAE. 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.	*To align with new sponsor standard safety reporting language*

4.Review each SAE report and evaluate the relationship of the SAE to HZN-825.	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. 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.	
Section 9.5.3.1.6 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 outcome is known.	**Section 9.5.3.1.6 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 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.	*To align with new sponsor standard safety reporting language*
Section 9.5.3.1.10 Development Safety Update Reports The Sponsor will prepare and submit annual safety reports to the US FDA. Developmental safety update reports will also be submitted to countries and territories as required.	**Section 9.5.3.1.10 Development Safety Update Reports** The Sponsor will prepare and submit Development Safety Update Reports (DSUR) to all relevant regulatory authorities in countries and regions where the trial is conducted. The Sponsor will prepare a single 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	*To add the development safety update report to align with recommendations from regulatory agencies and*

	include appropriate information on any other investigational products used in the clinical study, if applicable. **9.5.3.1.11 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. **9.5.3.1.12 Safety Monitoring Plan** Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.	*additional sections To align with new sponsor standard safety reporting language*

Section 9.5.3.2 Pregnancy and Lactation Reporting 9.5.3.2 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 [redacted], and results will be reported to the site. A urine pregnancy test will also be done at the Safety Follow-up Visit (whether at the clinic or at a remote site).	**Section 9.5.3.2 Pregnancy and Lactation Reporting** 9.5.3.2 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, urine pregnancy tests should also be done every 4 weeks after Day 1, which includes both in-clinic testing at scheduled visits prior to dosing [redacted] and at home (±7 day window) by the subject and reported to the site [redacted] A urine pregnancy test will also be done at the Safety Follow-up Visit (whether at the clinic or at a remote site).	*To align with new sponsor standard safety reporting language*
Section 9.5.3.2 Pregnancy and Lactation 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. 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 and the outcome of the pregnancy should be reported to the Sponsor.	**Section 9.5.3.2 Pregnancy and Lactation 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. 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	*To align with new sponsor standard safety reporting language*

	and no later than 24 hours of the Investigator's awareness of the event.	
Section 9.5.3.8 Laboratory Tests for Evaluation 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 9.5.3.8 Laboratory Tests for Evaluation** 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. [redacted]	*To provide additional guidance to promote subject safety*
Section 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.	**Section 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: • Good Clinical Practice (GCP) • the clinical trial protocol • an applicable regulation	*To update requirements for Principal Investigator responsibilities to report serious breaches per regulatory recommendations*

	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	
Section 17.1 Administrative Appendix Medical Monitor: [redacted], MD Associate Medical Director Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015 Business telephone number: [redacted] Email: [redacted] Sponsor Representative: [redacted] Sr. Manager, Clinical Operations Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015 Business telephone number: [redacted] Email: [redacted] 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	**Section 17.1 Administrative Appendix** Medical Monitor: [redacted], MD Medical Director Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015 Business 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] Sponsor Contact for Serious Adverse Event Reporting: Horizon Therapeutics U.S.A., Inc. US Fax: 1-888-814-8653 (toll free, within USA) Ex US Fax: +44 (0)207-136-1046 Email (worldwide): svc-ags-in-us@amgen.com	*To update key contact information*

Section 17.14 [redacted] Version dated 28 Feb 2022.	**Section 17.14** [redacted] Updated to version dated 14 June 2023.	*To align with latest guidance*
Section 17.15 Detailed Requirements for the Evaluation of Patients Detected with Abnormal Liver Function Test (new)	**Section 17.15 Detailed Requirements for the Evaluation of Patients Detected with Abnormal Liver Function Test (new)** Per protocol Section 9.3.3.1, 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. **An increase of serum aminotransferases to >3 × ULN and/or TBL >2 × ULN should be followed by repeat testing (ALT, AST, alkaline phosphatase, and TBL at minimum) within 48 to 72 hours to confirm the abnormality*.** A confirmed ALT/AST >3 × ULN and/or TBL >2 × ULN should be considered to record as AE. Please reach out to the Medical Monitor via Electronic Protocol Inquiry Platform to inform such events. It is critical to exclude the other possible causes of increased liver enzymes. If needed, please consider hepatologist/gastroenterologist consultation early in the evaluation. Additional imaging and laboratory tests (e.g., abdominal ultrasound, Hepatitis panel testing, etc.), as deemed necessary, should be performed to ascertain the etiology. Below are the requirements which need to be followed to ensure the close observation of patients who have confirmed ALT or AST levels >3 × ULN and/or TBL >2 × ULN: • Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. • Obtaining a more detailed history of symptoms and prior or concurrent diseases. • Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary	*To align with guidance from regulatory agencies and sponsor.*

	supplement preparations), alcohol use, recreational drug use, and special diets. • Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease. • Obtaining a history of exposure to environmental chemical agents. • Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin). • Considering gastroenterology or hepatology consultations. *If it is difficult for the subjects to return to the trial site promptly, the repeat test can be analyzed locally, but normal laboratory ranges should be recorded. Results should be made available to trial Investigators immediately and the data should be included in the case report forms. The subject should return to the site for the lab testing as soon as possible.	

2 SYNOPSIS

Protocol Title: A Multicenter, Open-label Extension Trial to Evaluate the Efficacy, Safety and Tolerability of HZN-825 in Patients with Diffuse Cutaneous Systemic Sclerosis	
Protocol Number: HZNP-HZN-825-302	**Phase**: 2b
Protocol Version: 3.0	
Test Drug: Fipaxalparant (HZN-825)	**Indication**: Systemic sclerosis
Number and Country of Trial Sites: Up to 135 sites globally	

Objectives:

The overall objective is to investigate the efficacy, safety and tolerability of fipaxalparant (HZN-825), a selective antagonist of lysophosphatidic acid receptor-1 ($LPAR_1$), administered twice daily (BID) to subjects with diffuse cutaneous systemic sclerosis (diffuse cutaneous SSc) in a 52-week open-label extension following completion of the randomized, double-blind, 52-week clinical trial (HZNP-HZN-825-301).

Two types of Baseline are defined:

- Trial Baseline, defined as the latest measurement prior to the first dose of fipaxalparant (HZN-825) in this extension trial
- Fipaxalparant (HZN-825) Baseline, defined as the latest measurement prior to the first dose of the trial drug in Trial HZNP-HZN-825-301.

Primary Objectives

- The primary efficacy objective is to assess the efficacy of 52 weeks of open-label treatment with fipaxalparant (HZN-825) in subjects with diffuse cutaneous SSc, as measured by change from both Baselines in forced vital capacity (FVC) % predicted.
- The primary safety objective is to examine the safety and tolerability of 52 weeks of open-label treatment with fipaxalparant (HZN-825), inclusive of, but not limited to, adverse events (AEs), serious AEs and the adverse event of special interest (AESI), from Day 1 to 4 weeks after last dose.

Exploratory Objectives

The exploratory objectives are to evaluate the following after 52 weeks of open-label treatment with fipaxalparant (HZN-825):

- Change from both Baselines in the modified Rodnan skin score (mRSS), the Revised Composite Response Index in Systemic Sclerosis (Revised CRISS [CRISS 25]), Health Assessment Questionnaire - Disability Index (HAQ-DI); Clinician Global Assessment (CGA); Patient Global Assessment (PTGA); the Physical Effects and Physical Limitations subscales of the scleroderma skin patient-reported outcome (SSPRO-18); proportion of subjects with clinically important change in the mRSS; American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from each Baseline in mRSS, HAQ-DI, PTGA, CGA and FVC % predicted; the SSPRO-18; the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0); Raynaud's phenomenon using the Raynaud's Assessment; the Scleroderma HAQ (SHAQ); Systemic Sclerosis Quality of Life Questionnaire (SScQoL); SF-12® Health Survey (SF-12); pain and pain component scale scores; fatigue based on the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F); lung fibrosis in subjects with suitable baseline high-resolution computed tomography (HRCT); diffusing capacity of the lungs for carbon monoxide (DLCO); serum and plasma biomarkers associated with $LPAR_1$ pathway, inflammation and/or fibrosis; and [redacted].
- The pharmacokinetics (PK) of fipaxalparant (HZN-825).

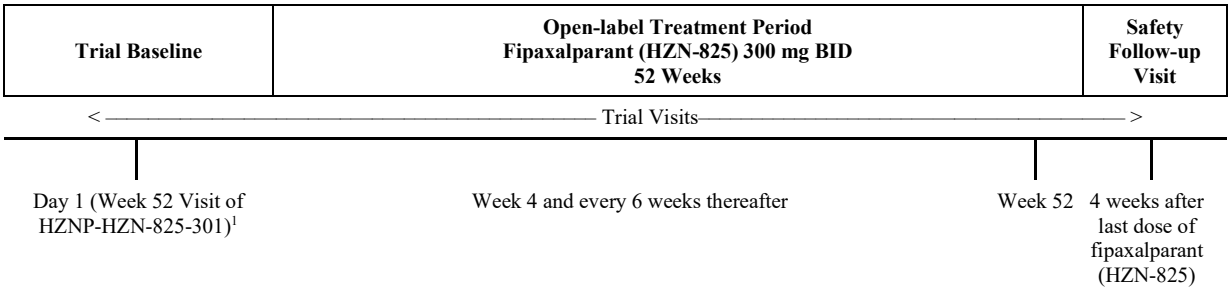
Trial Design:

This is an open-label, repeat-dose, multicenter extension trial of HZNP-HZN-825-301. Subjects who complete the double-blind Treatment Period (Week 52) in Trial HZNP-HZN-825-301 will be eligible to enter this 52-week extension trial. Subjects entering this extension trial will complete the Week 52 Visit activities in HZNP-HZN-825-301 and will not complete the Safety Follow-up Visit 4 weeks after the last dose of trial drug in HZNP-HZN-825-301. All HZNP-HZN-825-301 Week 52 assessments should be performed before the first dose of the extension trial drug is administered.

On Day 1 (Week 52 Visit of HZNP-HZN-825-301), subjects will receive their first dose of fipaxalparant (HZN-825) in this extension trial at the clinic and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. The Week 52 Visit activities in HZNP-HZN-825-301 will serve as Trial Baseline for this extension 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 return for a clinic visit and undergo the Week 52 assessments. Subjects will participate in a Safety Follow-up Visit 4 weeks after the last dose of fipaxalparant (HZN-825).

An overview of the trial design is presented in the schematic below.



BID=twice daily

1. All HZNP-HZN-825-301 Week 52 assessments should be performed before the first dose of the extension trial drug is administered.

Subject Population:

Inclusion Criteria:

1. Written informed consent.
2. Completed the double-blind Treatment Period (Week 52) in Trial HZNP-HZN-825-301; subjects prematurely discontinued from trial drug in Trial HZNP-HZN-825-301 for reasons other than safety or toxicity can be included at the discretion of the Investigator after completing Trial HZNP-HZN-825-301 scheduled visits, including Week 52 assessments.
3. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

Exclusion 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-825-301 (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
3. 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. 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. 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.
4. Pregnant or lactating women.
5. Any new development with the subject's disease or condition or any significant laboratory test abnormality during the course of Trial HZNP-HZN-825-301 that, in the opinion of the Investigator, would potentially put the subject at unacceptable risk.
6. Subjects will be ineligible if, in the opinion of the Investigator, they are unlikely to comply with the trial protocol or have a concomitant disease or condition that could interfere with the conduct of the trial.

Dose Regimen/Route of Administration:

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.

Dosage Form, Strength, Formulation and Storage:

Fipaxalparant (HZN-825) 150 mg tablets will be used in this trial and will be packaged in blister packs. The film-coated tablets are stored at controlled room temperature (20ºC to 25Cº, 68ºF to 77Fº).

Duration of Treatment and Follow-up:

The duration of the Treatment Period is 52 weeks. Subjects will participate in a Safety Follow-up Visit 4 weeks after the last dose of fipaxalparant (HZN-825).

Criteria for Evaluation:

Details of time points for trial activities and assessments are provided in Section 2.1.

Efficacy will be assessed by change in FVC % predicted, CGA, mRSS, ACR-CRISS, patient-reported outcomes (HAQ-DI, SHAQ global questions, PTGA, SSPRO-18, UCLA SCTC GIT 2.0 and Raynaud's Assessment), quality-of-life, health status and fatigue evaluations (SScQoL, SF-12, pain scores, fatigue scores [FACIT-F]), HRCT and DLCO.

Blood samples for fipaxalparant (HZN-825) PK assessment, autoantibodies and biomarkers associated with the $LPAR_1$ pathway, inflammation and/or fibrosis will be collected.

Safety will be assessed via AEs, concomitant medication use, physical examinations, vital signs, [redacted], laboratory evaluations and 12-lead electrocardiogram (ECG).

Statistical Analyses:

Primary Efficacy Endpoint

Change from both Baselines in FVC % predicted at Week 52.

Exploratory Efficacy Endpoints

1. Change from both Baselines in the mRSS at Week 52.
2. Proportion of subjects responding to treatment based on CRISS 25 at Week 52.
3. Change from both Baselines in HAQ-DI at Week 52.
4. Change from both Baselines in CGA at Week 52.
5. Change from both Baselines in PTGA at Week 52.
6. Change from both Baselines in the Physical Effects subscale of the SSPRO-18 at Week 52.
7. Change from both Baselines in the Physical Limitations subscale of the SSPRO-18 at Week 52.
8. Proportion of subjects with an mRSS decrease of ≥5 points and 25% from both Baselines at Week 52.
9. Responder rate (defined as ACR-CRISS [predicted probability] of at least 0.6) at Week 52.
10. Change from both Baselines in the SSPRO-18 at Week 52.
11. Change from both Baselines in each scale of the UCLA SCTC GIT 2.0 and the total GIT score at Week 52.
12. Change from both Baselines in Raynaud's phenomenon using the Raynaud's Assessment at Week 52.
13. Change from both Baselines in the SHAQ at Week 52.
14. Change from both Baselines in SScQoL scores at Week 52.
15. Change from both Baselines in SF-12 scores at Week 52.
16. Change from both Baselines in pain and pain component scale scores at Week 52.
17. Change from both Baselines in the FACIT-F score at Week 52.
18. Change from both Baselines in lung fibrosis based on HRCT at Week 52.
19. Change from both Baselines in DLCO at Week 52.
20. Change from both Baselines in serum and plasma biomarkers associated with $LPAR_1$ pathway, inflammation and/or fibrosis at [redacted]
21. Change from both Baselines in [redacted].

Safety and Tolerability Endpoints

1. Incidence of treatment-emergent adverse events (TEAEs) and the AESI [redacted].
2. Concomitant medication use.
3. Vital signs.
4. 12-lead ECGs.
5. Clinical safety laboratory evaluations.

Pharmacokinetic Endpoint

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

Statistical Analysis of Efficacy and Safety Parameters

Efficacy analyses will be performed on the full analysis set (FAS), consisting of all subjects who were enrolled (i.e., signed the informed consent form) and who received at least 1 dose or partial dose of fipaxalparant (HZN-825) in this extension trial. Subjects will be analyzed according to the treatment group to which they were randomized in the previous trial, 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 this extension trial. This analysis set will be analyzed according to the group determined by the treatment that the subject received in the previous trial and overall.

The Per-Protocol (PP) analysis set will consist of all subjects in the FAS with no major protocol violations. The PP analysis set will be used, as needed, for supportive analysis of the primary endpoint and potentially other key endpoints. Subjects in this analysis set will be analyzed according to the treatment group to which they were randomized in the previous, and combined into an 'overall' group.

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

Sample Size Estimate:
The sample size is based on the number of subjects who completed Trial HZNP-HZN-825-301.

2.1 Schedule of Assessments

	Open-label Treatment Period (Fipaxalparant [HZN-825] 300 mg BID)										Safety Follow-up Visit
Trial Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 4 weeks after last dose of fipaxalparant (HZN-825)**
Trial Week (W)	**Day 1 [2]**	**W4**	**W10 [1]**	**W16**	**W22 [1]**	**W28**	**W34 [1]**	**W40**	**W46 [1]**	**W52/ PD**	
Visit Window (±days)		**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±14)**
Informed consent	X										
Review eligibility criteria	X										
Weight	X [3]					X				X	
Fipaxalparant (HZN-825) dispensing	X	X	X	X	X	X	X	X	X		
Compliance		X	X	X	X	X	X	X	X	X	
mRSS [4]	X [3]			X		X		X		X	
FVC % predicted/spirometry [4]	X [3]			X		X		X		X	
CGA	X [3]			X		X		X		X	
Lung HRCT	X [3]									X [5]	
DLCO	X [3]					X [6]				X [6]	
Patient-reported outcome assessments											
SHAQ	X [3]			X		X		X		X	
PTGA	X [3]			X		X		X		X	
UCLA SCTC GIT 2.0	X [3]					X				X	
SSPRO-18	X [3]					X				X	
SScQoL	X [3]					X				X	
SF-12	X [3]					X				X	
Pain questionnaire	X [3]					X				X	
Fatigue (FACIT-F)	X [3]					X				X	
Raynaud's assessment [7]	X [3]				X				X		

	Open-label Treatment Period (Fipaxalparant [HZN-825] 300 mg BID)										Safety Follow-up Visit
Trial Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 4 weeks after last dose of fipaxalparant (HZN-825)**
Trial Week (W)	**Day 1 [2]**	**W4**	**W10 [1]**	**W16**	**W22 [1]**	**W28**	**W34 [1]**	**W40**	**W46 [1]**	**W52/ PD**	
Visit Window (±days)		**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±14)**
Anchor questions											
ACR-CRISS (last week)	X [3]			X		X		X		X	
ACR-CRISS (overall health and change since start of trial)						X				X	
FVC (last week)	X [3]			X		X		X		X	
FVC (change since start of trial)	X [3]					X				X	
HAQ-DI (last week)	X [3]			X		X		X		X	
HAQ-DI (change since start of trial)						X				X	
SSPRO-18 (last week)	X [3]					X				X	
SSPRO-18 (change since start of trial)						X				X	
Pregnancy test [8]	[redacted]										
Physical examination [9]	X [3]					X				X	X
Vital signs [10]	X [3]	X	X	X	X	X	X	X	X	X	X
[redacted]											
12-lead electrocardiogram [11]	X [3]	X		X		X				X	
Echocardiogram [11]	X										
Clinical laboratory safety tests [12]											
Chemistry	X [3]	X	X	X	X	X		X		X	X
Lipids	X [3]					X				X	
Hematology	X [3]	X	X	X	X	X		X		X	X
Urinalysis	X [3]	X	X	X	X	X		X		X	X
ESR [13] and hsCRP	X [3]									X	X
Autoantibodies [14]	X [3]									X	
PK samples [15]	X [3]	X		X		X		X			

	Open-label Treatment Period (Fipaxalparant [HZN-825] 300 mg BID)										Safety Follow-up Visit
Trial Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 4 weeks after last dose of fipaxalparant (HZN-825)**
Trial Week (W)	**Day 1 [2]**	**W4**	**W10 [1]**	**W16**	**W22 [1]**	**W28**	**W34 [1]**	**W40**	**W46 [1]**	**W52/ PD**	
Visit Window (±days)		**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±14)**
Serum biomarkers [16]	[redacted]										
Plasma biomarkers [16]											
Adverse event assessment [17]	X	X	X	X	X	X	X	X	X	X	X
Prior/ concomitant medications [18]	X [3]	X	X	X	X	X	X	X	X	X	X

ACR-CRISS=American College of Rheumatology-Composite Response Index in Systemic Sclerosis; BID=twice daily; CGA=Clinician Global Assessment; DLCO=diffusing capacity of the lungs for carbon monoxide; ESR=erythrocyte sedimentation rate; FACIT-F=Functional Assessment of Chronic Illness Therapy – Fatigue Scale; FVC=forced vital capacity; HAQ-DI=Health Assessment Questionnaire – Disability Index; HRCT=high-resolution computed tomography; hsCRP=high-sensitivity C-reactive protein; mRSS=modified Rodnan skin score; PD=premature discontinuation; PK=pharmacokinetic; PTGA=Patient Global Assessment; SF-12=SF-12® Health Survey; SHAQ=Scleroderma Health Assessment Questionnaire; SScQoL=Systemic Sclerosis Quality of Life Questionnaire; SSPRO-18=scleroderma skin patient-reported outcome; UCLA SCTC GIT 2.0=University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract; W=Week; WOCBP=women of childbearing potential

1. Visits may be conducted as home health visits, as available within local regions.
2. On Day 1 (Baseline), subjects will receive the first dose of fipaxalparant (HZN-825) in this extension trial in the clinic. All Day 1 assessments should be performed before the first dose of trial drug is administered in the clinic.
3. Performed as part of the Week 52 Visit of HZNP-HZN-825-301; if applicable, the result will be considered a Trial Baseline value for this extension trial.
4. Except when strictly unavoidable, the same person should perform the assessment at each evaluation during the trial. The mRSS assessment should be performed by a qualified Investigator (or designee).
5. The lung HRCT scan should be performed within ±2 weeks of the Week 52/PD Visit.
6. DLCO can be assessed within ±2-weeks of the Week 28 and Week 52/PD Visits.
7. Daily electronic diaries will be completed for 4 weeks starting on Day 1, 4 weeks starting at the Week 22 Visit and 4 weeks starting at the Week 46 Visit.
8. Perform for WOCBP. Serum pregnancy test at [redacted] (or as needed). Urine pregnancy tests should also be done every 4 weeks after Day 1, which includes both in-clinic testing at scheduled visits prior to dosing [redacted] and at home (also a ±7-day window) by the subject and reported to the site [redacted] A urine pregnancy test will also be done at the Safety Follow-up Visit.
9. A complete physical examination, including but not limited to cardiac, pulmonary, neurologic and skin assessments, as well as directed rheumatology assessments [redacted]
10. Vital signs (blood pressure, heart rate, respiratory rate, temperature) will be measured at each visit.
11. Additional electrocardiograms or echocardiograms will be conducted, if clinically indicated. A standard transthoracic echocardiogram will be conducted on Day 1. However, an echocardiogram that has been performed during HZNP-HZN-825-301 and within the 3 months prior to HZNP-HZN-825-302 Day 1 can serve as the Trial Baseline echocardiogram if the subject has been clinically stable.
12. See Section 9.5.3.8 for details.
13. ESR must be processed within 1 hour of the blood draw.

14. Autoantibodies include anti-centromere antibody, anti-RNA polymerase antibody, anti-topoisomerase 1 and anti-U1 small nuclear ribonucleoprotein.
15. PK samples will be collected at each of the following visits: Day 1 (pre-dose), Week 4 (pre-dose and 2 to 4 hours post-dose) and Weeks 16, 28 and 40 (pre-dose). Note: all pre-dose samples will be collected prior to any fipaxalparant (HZN-825) administration for the day.
16. Blood samples will be collected for serum and plasma biomarkers prior to dosing on Day [redacted] as well as at the [redacted] Visit.
17. Adverse events occurring or worsening after the first dose of fipaxalparant (HZN-825) on Day 1 through the Safety Follow-up Visit will be considered treatment-emergent adverse events for this trial. All adverse events that occur from the signing of informed consent through the Safety Follow-up Visit will be recorded. The subject should be assessed for the development of new onset of scleroderma renal crisis, new onset of left ventricular failure, new onset of pulmonary arterial hypertension or right heart catheterization requiring treatment, gastrointestinal dysmotility requiring enteral (tube feeding) or parenteral nutrition or digital ischemia with gangrene, amputation or hospitalization requiring treatment.
18. 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
ACR-CRISS	American College of Rheumatology-Composite Response Index in Systemic Sclerosis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
$AUC_{0\text{-}12h}$	area under the concentration-time curve from 0 to 12 hours
BID	twice daily
CFR	Code of Federal Regulations
CGA	Clinician Global Assessment
C_{max}	maximum observed concentration
CRISS 25	Composite Response Index in Systemic Sclerosis 25
C_{trough}	trough concentration
[redacted]	
DOCA	deoxycorticosterone acetate
DLCO	diffusing capacity of the lungs for carbon monoxide
DSUR	Development Safety Update Report
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FAS	full analysis set
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HRCT	high-resolution computed tomography
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Definition
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IND	Investigational New Drug
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
LPA	lysophosphatidic acid
$LPAR_1$	lysophosphatidic acid receptor 1
mRSS	modified Rodnan skin score
OAT	organic anion transporter
PAH	pulmonary arterial hypertension
PK	pharmacokinetic
PTGA	Patient Global Assessment
QD	once daily
Revised CRISS	Revised Composite Response Index in Systemic Sclerosis
SAE	serious adverse event
SF-12	SF-12® Health Survey
SHAQ	Scleroderma Health Assessment Questionnaire
SSc	systemic sclerosis
SScQoL	Systemic Sclerosis Quality of Life Questionnaire
SSPRO-18	scleroderma skin patient-reported outcome
TBL	total bilirubin
TEAE	treatment-emergent adverse event
UCLA SCTC GIT 2.0	University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract
ULN	upper limit of normal
US	United States
U.S.A.	United States of America
VAS	visual analog scale
WOCBP	women of childbearing potential

Abbreviations that appear only in tables or in a single paragraph are defined with the relevant 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 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for review and approval/favorable opinion. A letter confirming the IRB/IEC approval/favorable opinion of the protocol, the subject ICF and applicable trial documentation, a list of the IRB/IEC members involved in the vote, as well as a statement that the IRB/IEC 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 IRB/IEC 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.

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 IRB/IEC`s 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, IRB/IEC 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 up to 135 trial sites globally; the Coordinating Investigator will be [redacted], MD, MSc (Table 6.1). 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	Person/Organization
Coordinating Investigator	[redacted], MD, MSc
Contract research organization (project management, monitoring and statistical analysis)	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

7 INTRODUCTION

7.1 Background

7.1.1 Diffuse Cutaneous Systemic Sclerosis

The term scleroderma is used to describe the presence of thickened, hardened skin. Scleroderma is the cardinal feature of systemic sclerosis (SSc). Patients with SSc are commonly classified into 2 distinct subsets on the basis of the pattern of skin involvement. Diffuse cutaneous SSc is dominated by rapidly progressive fibrosis of the skin, lungs and other internal organs. By contrast, limited cutaneous SSc is dominated by vascular manifestations and skin and organ fibrosis is generally limited and slow to progress [Varga and Abraham, 2007]. SSc has a worldwide distribution and is more frequent in women than men [Mayes et al., 2003]. Based on incidence and survival rates, an estimated 75,000 to 100,000 individuals in the US have SSc [Varga and Abraham, 2007].

The involvement of multiple organs is the distinguishing hallmark of diffuse cutaneous SSc and accounts for much of the morbidity and mortality associated with the disease [Varga and Abraham, 2007; Asano, 2017; Volkmann and Varga, 2019]. Immune perturbations and vascular injury precede and contribute to the development of fibrosis, which, in turn, further exacerbates vascular and immune damage [Varga and Abraham, 2007; Bhattacharyya et al., 2011; Asano and Sato, 2015; Volkmann and Varga, 2019]. The disease is considered incurable and diffuse cutaneous SSc carries the highest risk of fatality of the connective tissue diseases, with 55% survival at 10 years [Mayes et al., 2003; Varga and Abraham, 2007].

There is no clear understanding of the initial disease triggers but it is generally accepted that genetic, epigenetic modifications and/or environmental factors cause an injury to the vasculature leading to a complex pathogenesis involving immune activation, inflammation, small vessel damage and an increase in the synthesis and deposition of extracellular matrix components resulting in multiorgan fibrosis [Asano and Sato, 2015; Asano, 2017; Volkmann and Varga, 2019]. This complex pathogenesis includes but is not limited to activation of dermal fibroblasts, skewing of T helper populations to a Th2/Th17 phenotype, differentiation of macrophages to an M2 phenotype, increased infiltration of plasmacytoid dendritic cells, endothelial-to-mesenchymal transition, epithelial cell activation and differentiation of various cell types into myofibroblasts [Asano, 2017].

SSc is highly heterogeneous in its multisystem clinical manifestations, including Raynaud's phenomenon, cutaneous telangiectasia, nail fold capillary alterations, pulmonary arterial hypertension (PAH), gastric antral vascular ectasia and scleroderma renal crisis with malignant hypertension [Varga and Abraham, 2007]. The disease severity varies among patients and follows a variable and unpredictable course and response to treatment [Varga and Abraham, 2007; Bhattacharyya et al., 2011; Volkmann and Varga, 2019]. The complexity and heterogeneity of the disease pose unique challenges for the development of effective therapies.

7.1.2 Lysophosphatidic Acid Receptor 1 ($LPAR_1$)

Lysophosphatidic acid (LPA) signaling has been associated with skin, pulmonary, cardiac, peritoneal and tubulointerstitial fibrosis, and may be a new therapeutic target for treating fibrotic diseases, including SSc. LPA is a bioactive phospholipid that regulates diverse cellular processes, including cell motility, proliferation, chemotaxis, survival and differentiation through binding to and activating a family of 6 specific G protein-coupled receptors ($LPAR_1$ to $LPAR_6$) [Chun et al., 2002]. LPA levels are increased in biological fluids of patients with inflammatory or fibrotic diseases, including SSc [Tager et al., 2008; Tokumura et al., 2009].

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 idiopathic pulmonary fibrosis (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].

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.

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

[redacted]

7.1.3.3 Nonclinical Pharmacokinetics

[redacted]

7.1.3.4 Clinical Experience

Fipaxalparant (HZN-825) has been administered to 244 healthy subjects in 9 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 PK 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 (SHAQ), overall disease severity and pruritus [Allanore et al., 2018].

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.

[redacted] Additionally, increases in [redacted] 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

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 [redacted], 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 [redacted], postural dizziness, flatulence and abdominal pain were slightly more frequent in fipaxalparant (HZN-825)-treated than in placebo-treated subjects. [redacted] 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).

AESIs are considered monitorable. Taking into account mitigation measures to minimize risk to subjects in this trial, the potential risk 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 subjects.

More detailed information on the benefits and risks of fipaxalparant (HZN-825) is provided in the Investigator's Brochure Section 6.2 and Section 12.

7.2 Rationale for this Trial

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

This trial is designed as an open-label extension of HZNP-HZN-825-301, in which subjects received fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (HZN-825) 300 mg BID or placebo during the 52-week double-blind Treatment Period. Subjects in this extension trial will receive open-label fipaxalparant (HZN-825) 300 mg BID. This extension trial 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. This trial will 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 HZNP-HZN-825-301 and evaluation of efficacy in subjects who received placebo in HZNP-HZN-825-301.

7.3 Rationale for Dose Selection

The dose regimen to be evaluated in this trial is 300 mg BID taken with a meal using fipaxalparant (HZN-825) tablets manufactured by [redacted] and [redacted]. This regimen was 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. The observed mean steady-state trough concentration (C_{trough}) was 7300 ng/mL in the Phase 2a trial.

Based on preliminary PK results from Trial HZNP-HZN-825-101, 300 mg BID dosing with a meal using fipaxalparant (HZN-825) [redacted] tablets is expected to achieve similar steady-state C_{trough} as observed in the Phase 2a trial in subjects with SSc and above the values based on in vitro potency evaluations. Additionally, after adjusting for plasma protein binding of fipaxalparant (HZN-825) between humans and rats (99.97% and 99.92%, respectively), 300 mg BID is 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 exposure associated with fipaxalparant (HZN-825) 300 mg BID is anticipated to be well tolerated and have clinical efficacy.

8 TRIAL OBJECTIVES

The overall objective is to investigate the efficacy, safety and tolerability of fipaxalparant (HZN-825), a selective antagonist of $LPAR_1$, administered BID to subjects with diffuse cutaneous SSc in a 52-week open-label extension following completion of the randomized, double-blind, 52-week clinical trial (HZNP-HZN-825-301).

Two types of Baseline are defined:

- Trial Baseline, defined as the latest measurement prior to the first dose of fipaxalparant (HZN-825) in this extension trial
- Fipaxalparant (HZN-825) Baseline, defined as the latest measurement prior to the first dose of the trial drug in Trial HZNP-HZN-825-301.

8.1 Primary Objectives

- The primary efficacy objective is to assess the efficacy of 52 weeks of open-label treatment with fipaxalparant (HZN-825) in subjects with diffuse cutaneous SSc, as measured by change from both Baselines in FVC % predicted.
- The primary safety objective is to examine the safety and tolerability of 52 weeks of open-label treatment with fipaxalparant (HZN-825), inclusive of, but not limited to, AEs, SAEs and the AESI, from Day 1 to 4 weeks after last dose.

8.2 Exploratory Objectives

The exploratory objectives are to evaluate the following after 52 weeks of open-label treatment with fipaxalparant (HZN-825):

- Change from both Baselines in the mRSS, the Revised CRISS (CRISS 25), HAQ-DI; Clinician Global Assessment (CGA); Patient Global Assessment (PTGA); the Physical Effects and Physical Limitations subscales of the scleroderma skin patient-reported outcome (SSPRO-18); proportion of subjects with clinically important change in the mRSS; American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from each Baseline in mRSS, HAQ-DI, PTGA, CGA and FVC % predicted; the SSPRO-18; the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0); Raynaud's phenomenon using the Raynaud's Assessment; the SHAQ; Systemic Sclerosis Quality of Life Questionnaire (SScQoL); SF-12® Health Survey (SF-12); pain and pain component scale scores; fatigue based on the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F); lung fibrosis in subjects with suitable baseline high-resolution computed tomography (HRCT); diffusing

capacity of the lungs for carbon monoxide (DLCO); serum and plasma biomarkers associated with $LPAR_1$ pathway, inflammation and/or fibrosis; and [redacted]

- The PK of fipaxalparant (HZN-825).

9 INVESTIGATIONAL PLAN

9.1 Overall Trial Design and Plan

This trial will be conducted at up to 135 sites globally.

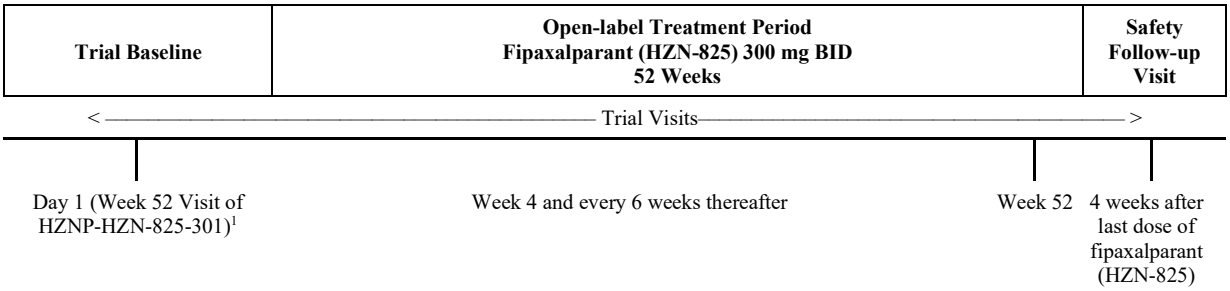
This is an open-label, repeat-dose, multicenter extension trial of HZNP-HZN-825-301. Subjects who complete the double-blind Treatment Period (Week 52) in Trial HZNP-HZN-825-301 will be eligible to enter this 52-week extension trial. Subjects entering this extension trial will complete the Week 52 Visit activities in HZNP-HZN-825-301 and will not complete the Safety Follow-up Visit 4 weeks after the last dose of trial drug in HZNP-HZN-825-301. All HZNP-HZN-825-301 Week 52 assessments should be performed before the first dose of the extension trial drug is administered.

On Day 1 (Week 52 Visit of HZNP-HZN-825-301), subjects will receive their first dose of fipaxalparant (HZN-825) in this extension trial at the clinic and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. The Week 52 Visit activities in HZNP-HZN-825-301 will serve as Trial Baseline for this extension 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 return for a clinic visit and undergo the Week 52 assessments. Subjects will participate in a Safety Follow-up Visit 4 weeks after the last dose of fipaxalparant (HZN-825).

An overview of the trial design is presented in Figure 9.1 and details of trial activities are provided in Section 2.1, *Schedule of Assessments*.

Figure 9.1 Schematic of Trial Design



BID=twice daily
1. All HZNP-HZN-825-301 Week 52 assessments should be performed before the first dose of the extension trial drug is administered.

9.2 Discussion of Trial Design

This trial is an open-label, repeat-dose, multicenter extension trial in the diffuse cutaneous SSc population 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 is typically the common length of exposure to trial drug in randomized, double-blind, placebo-controlled clinical trials of SSc [Del Galdo et al., 2020; Pope, 2020] and reflects the length of time needed to see convincing clinical benefits. Receipt of placebo longer than 12 months may not be ethical in subjects with diffuse cutaneous SSc in particular, since this patient population is enriched for a worse prognosis across multiple body systems. Since clinically important detectable improvements may require an even longer duration of treatment [Pope, 2020], this extension trial 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. 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 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) in Trial HZNP-HZN-825-301; subjects prematurely discontinued from trial drug in Trial HZNP-HZN-825-301 for reasons other than safety or toxicity can be included at the discretion of the Investigator after completing Trial HZNP-HZN-825-301 scheduled visits, including Week 52 assessments.
3. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

9.3.2 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-825-301 (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
3. 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. 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. 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.

4. Pregnant or lactating women.
5. Any new development with the subject's disease or condition or any significant laboratory test abnormality during the course of Trial HZNP-HZN-825-301 that, in the opinion of the Investigator, would potentially put the subject at unacceptable risk.
6. Subjects will be ineligible if, in the opinion of the Investigator, they are unlikely to comply with the trial protocol or have 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 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 will participate in a Safety Follow-up Visit 4 weeks after the last dose of fipaxalparant (HZN-825).

9.3.3.1 Removal of Subjects from Treatment

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/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 the 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:
    - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN)
    - ALT or AST >5 × ULN for more than 2 weeks

- ALT or AST >3 × ULN and (total bilirubin [TBL] >2 × ULN or international normalized ratio >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 (refer to Appendix 17.15). 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 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.
- Restricted medications. Initiation of any therapy prohibited in the trial per Table 9.1 may lead to subject discontinuation from treatment. The Investigator may consult with the trial Medical Monitor before initiation of the restricted or rescue medications.
- Withdrawal by subject/guardian. 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, IRB/IEC or regulatory agency terminates the trial.
- Pregnancy.
- 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 Open-label 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.

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 trial, including the Safety Follow-up Visit.
- Trial terminated by Sponsor.

9.3.4 Discontinuation of 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
- Withdrawal of the license to manufacture (and/or of the permission to import)

9.3.5 Replacement Policy

9.3.5.1 Subjects

No subject prematurely discontinued from the trial for any reason will be replaced.

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 reason:

- Unacceptable protocol adherence.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will receive fipaxalparant (HZN-825) 300 mg BID for 52 weeks.

9.4.2 Identity of Investigational Product

[redacted]

9.4.3 Labeling

Fipaxalparant (HZN-825) 150 mg tablets will be packaged in blister packs in compliance with Sponsor/contract research organization standard procedures and all local requirements. Each blister pack label will be labeled with a unique number.

Upon arrival of fipaxalparant (HZN-825) tablet 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 fipaxalparant (HZN-825) tablets and must maintain adequate records of the receipt and disposition of all fipaxalparant (HZN-825) tablets 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 fipaxalparant (HZN-825).

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 fipaxalparant (HZN-825) tablets 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) 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 such that 4 tablets (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

Any completely missed dose should be recorded on the *Dosing Interruptions* eCRF.

[redacted]

9.4.6.1.2 Drug-induced Liver Injury

Elevated [redacted] have been evaluated to be an important identified risk with fipaxalparant (HZN-825). The events are mostly non-serious and reversible. 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

All subjects will receive fipaxalparant (HZN-825) 300 mg BID in this open-label extension trial.

9.4.8 Blinding and Unblinding

This is an open-label extension trial.

9.4.9 Concomitant Therapy and Restricted Medications

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

Table 9.1 Restricted Medications

Medication	Restricted Time Period
Steroids for conditions other than diffuse cutaneous SSc	Throughout the trial. 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.
Oral or parenteral therapy approved for PAH	Receipt of no more than 1 approved therapy during the trial. Parenteral therapy is not allowed (therapy is allowed for erectile dysfunction and/or Raynaud's phenomenon/digital ulcers).
Use of any non-steroid immunosuppressive agent, small biologic molecule, cytotoxic or anti-fibrotic drug, including [redacted] or other immunosuppressive or cytotoxic medication other than mycophenolate mofetil, mycophenolic acid, low-dose prednisone or an anti-malarial	Throughout the trial.
United States Food and Drug Administration-approved agent for SSc or an investigational agent	Throughout the trial.
Drug/alcohol abuse	Throughout the trial.
[redacted]	

[redacted] PAH=pulmonary arterial hypertension; SSc=systemic sclerosis

[redacted]

In case of a clinically significant deterioration in SSc, initiation of additional therapy or change in dose of background therapy is allowed following consultation with the trial Medical Monitor. If the additional therapy had been already initiated for clinically significant deterioration during the course of Trial HZNP-HZN-825-301, it can be continued. The addition or change of background therapy for diffuse cutaneous SSc due to clinical deterioration will be referred to as "rescue therapy." Detailed (S)AE information following such events should be recorded in the eCRF.

[redacted]

[redacted] or organic anion transporter (OAT)1/OAT3 that have narrow therapeutic windows.

[redacted] Fipaxalparant (HZN-825) is an in vitro inhibitor of OAT1 and OAT3 and may increase the systemic exposures of methotrexate.

Clinically significant deterioration includes:

- An absolute decline since Trial Baseline in FVC % predicted ≥10% or an absolute decline since Trial Baseline in FVC % predicted ≥5 to 9% with associated decline in DLCO ≥15% since Trial Baseline, or
- Relative change since Trial Baseline in mRSS of >25% and an absolute change since Trial Baseline of >5 points, or
- Clinically significant deterioration in other organ systems or that does not meet above criteria, per Investigator assessment, may be appropriate (consultation with the Medical Monitor should occur prior).

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.

All concomitant treatment (for diffuse cutaneous SSc and other conditions), including herbs and supplements, must be documented in the eCRF.

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 fipaxalparant (HZN-825) 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, Pharmacokinetic and Safety Variables

Refer to the Schedule of Assessments (Section 2.1) 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.

Spirometry measurements must be performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) 2019 guidelines [Graham et al., 2019]. 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 as during Trial HZNP-HZN-825-301. 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.

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 Clinician Global Assessment

The CGA is also known as Physician Global Assessment (MDGA). The CGA is an 11-point Likert scale ranging from 0 to 10 (0=excellent to 10=extremely poor) on which the physician rates the subject's overall health over the past week. There is also a 5-point scale (from 1 to 5; 1=much better to 5=much worse) on which the physician rates the subject's overall scleroderma condition compared to the last clinic visit.

A copy of the CGA is provided in Section 17.2.

9.5.1.3 Modified Rodnan Skin Score

The mRSS is a validated method for estimating skin thickening. Seventeen different body areas are scored as normal (0), mild thickening (1), moderate thickening (2) and severe thickening (3), with a maximum score of 51. The assessment should be performed by a qualified Investigator (or designee). Except when strictly unavoidable, the same person should perform the assessment at each evaluation during the trial.

A copy of the form for assessing the mRSS is provided in Section 17.3.

9.5.1.4 American College of Rheumatology-Composite Response Index in Systemic Sclerosis

Subjects will be evaluated using the ACR-CRISS, an outcome measure for diffuse cutaneous SSc. The ACR-CRISS includes core items that assess change in 2 prominent manifestations of early diffuse cutaneous SSc (skin and interstitial lung disease [ILD]), functional disability (HAQ-DI) and patient and clinician global assessments. In addition, the score captures a clinically meaningful worsening of internal organ involvement requiring treatment.

The ACR-CRISS is a 2-step process that assigns a probability of improvement for a subject that ranges from 0.0 (no improvement) to 1.0 (marked improvement). Step 1 will be evaluated as part of the AE assessment, at which time the Investigator will assess if a subject has developed new or worsening cardiopulmonary and/or renal involvement due to SSc, as outlined below.

- New scleroderma renal crisis, defined as follows (adapted from Steen et al., 2003):
  Hypertensive scleroderma renal crisis:
  1. New onset hypertension, defined as any of the following:
     a. systolic blood pressure ≥140 mmHg
     b. diastolic blood pressure ≥90 mmHg
     c. rise in systolic blood pressure ≥30 mmHg

d. rise in diastolic blood pressure ≥20 mmHg

AND

2. One of the following 5 features:
   a. increase in serum creatinine by ≥50% over Baseline OR serum creatinine ≥120% of ULN for local laboratory
   b. proteinuria ≥2+ by dipstick
   c. hematuria ≥2+ by dipstick or ≥10 red blood cells/high-powered field
   d. thrombocytopenia: <100,000 platelets/mm^3
   e. hemolysis, defined as anemia not due to other causes and either of the following:
      1) schistocytes or other red blood cell fragments seen on blood smear
      2) increased reticulocyte count

Normotensive scleroderma renal crisis:

1. Increase in serum creatinine >50% over Baseline OR serum creatinine ≥120% of ULN for local laboratory:

AND

2. One of the following 5 features:
   a. proteinuria ≥2+ by dipstick
   b. hematuria ≥2+ by dipstick or ≥10 red blood cells/high-powered field
   c. thrombocytopenia: <100,000 platelets/mm^3
   d. hemolysis, defined as anemia not due to other causes and either of the following:
      1) schistocytes or other red blood cell fragments seen on blood smear
      2) increased reticulocyte count
   e. Renal biopsy findings consistent with scleroderma renal crisis (microangiopathy)

- Decline in FVC % predicted ≥15% (relative), confirmed by another FVC % within a month, HRCT to confirm ILD (if previous scan did not show ILD) and FVC % predicted <80%
- New onset of left ventricular failure (defined as ejection fraction ≤45%) requiring treatment
- New onset of PAH on right heart catheterization requiring treatment
- Gastrointestinal dysmotility requiring enteral (tube feeding) or parenteral nutrition
- Digital ischemia with gangrene, amputation or hospitalization requiring treatment

If a subject meets any of these criteria, the subject is assigned a probability of 0. Otherwise, in Step 2, the probability of improvement is calculated based on the 5 core measures incorporated into the ACR-CRISS, including changes in mRSS, FVC % predicted, HAQ-DI, PTGA and CGA [Khanna and Berrocal et al., 2016].

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

Rate the severity of your systemic sclerosis in the last week:

- 0: none
- 1: mild
- 2: moderate
- 3: severe
- 4: very severe

Rate the change in your overall health since you started 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

Rate the change in your systemic sclerosis since you started 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

9.5.1.5 Revised Composite Response Index in Systemic Sclerosis (CRISS 25)

The Revised CRISS (CRISS 25) is defined as improvement in at least 2 components: ≥5% increase for FVC % predicted and/or ≥25% decrease for mRSS, HAQ-DI, PTGA, CGA and worsening in no more than one component: ≥5% decrease percent predicted FVC and/or ≥25% increase for mRSS, HAQ-DI, PTGA, CGA, at 52 weeks. Revised CRISS (CRISS 25) is also a 2-step process. If the subject meets Step 1 (as defined in Section 9.5.1.4), they are considered

not improved, given a percentage change of 0% for each core set item. In Step 2, the five core set measures are individually collected and scored.

9.5.1.6 Plasma and Serum Biomarkers

Blood samples will be collected prior to dosing on [redacted] as well as at the [redacted] Visit for analysis of plasma and serum biomarkers associated with the $LPAR_1$ pathway, inflammation or fibrosis. Only subjects who were able to provide a Baseline blood sample in Trial HZNP-HZN-825-301 for serum and plasma biomarkers will have this assessment completed.

Examples of biomarkers that may be measured include, but are not limited to, proteins associated with the complement pathway and components of extracellular matrix pathways.

Instructions for processing, handling, storing and shipping of samples will be detailed in the laboratory manual that will be provided to each site. Samples will be collected, processed and stored at $\leq$-70^{o} C at the site until shipment to the central laboratory (PPD Central Laboratory). The central laboratory will store the samples at $\leq$-70^{o} C until shipment to the appropriate laboratory for testing. Based on the results of the above assays, other similar serum biomarkers may be assayed to further explore drug and disease mechanisms. Blood samples collected for analysis of biomarkers may be used for future testing should there be new information about the disease; however, the samples will not be stored for more than 5 years after the trial is completed. All samples will be destroyed after all potential biomarkers have been evaluated or 5 years after the trial is complete, whichever comes first.

9.5.1.7 Lung High-resolution Computed Tomography

Lung HRCT will be reviewed by a central reader.

9.5.1.8 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 when possible [Graham et al., 2017].

DLCO values will be adjusted for 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.

9.5.1.9 Patient-reported Outcome Assessments

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

9.5.1.9.1 Health Assessment Questionnaire – Disability Index

The HAQ-DI, which is part of the SHAQ (Section 9.5.1.9.4), assesses the subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip and usual activities [Cole et al., 2006]. The subject's ability to accomplish each activity in the past week is indicated as: without any difficulty, with some difficulty, with much difficulty and unable to do. Any devices that are usually used to complete activities and any categories for which help from another person is needed is also assessed.

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

How did your systemic sclerosis limit your daily activities in the last week?

- 0: did not limit activity
- 1: mildly limited my activity
- 2: moderately limited my activity
- 3: severely limited my activity
- 4: very severely limited my activity

How has limitation of your daily activities changed since the start of the trial?

- +3: very much less limited
- +2: much less limited
- +1: a little less limited
- 0: no change
- -1: a little more limited
- -2: much more limited
- -3: very much more limited

9.5.1.9.2 Patient Global Assessment

The PTGA is an 11-point Likert scale ranging from 0 to 10 (0=excellent to 10=extremely poor) on which the subject rates his/her overall health and illness-related pain level over the past week and how much the skin involvement due to scleroderma has interfered with daily activity and how rapidly the skin disease has been progressing over the past month. There is also a 5-point Likert scale (from 1 to 5; 1=much better to 5=much worse) on which the subject rates overall scleroderma skin involvement compared to the last clinic visit.

9.5.1.9.3 Scleroderma Skin Patient-reported Outcome Instrument

The SSPRO-18, developed through concept elicitation in patients with diffuse cutaneous and limited cutaneous SSC based on 3 focus groups, is an 18-item, patient-reported outcome

instrument that specifically assesses skin-related quality of life in patients with SSc and was developed with extensive patient input and according to the FDA patient-reported outcomes guidance [Man et al., 2017]. The SSPRO-18 comprises 4 major conceptual constructs—physical effects, emotional effects, physical limitations and social effects—and has reproducibility and high internal consistency. This instrument reflects how subjects feel and function from several different health perspectives. Good test-retest reliability and construct validity has been shown [Man et al., 2017]. Responsiveness has been shown for lenabasum vs placebo [Spiera et al., 2020].

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

How severely was your skin affected by systemic sclerosis in the last week?

- 0: My skin was not affected by systemic sclerosis.
- 1: My skin was mildly affected by systemic sclerosis.
- 2: My skin was moderately affected by systemic sclerosis.
- 3: My skin was severely affected by systemic sclerosis.
- 4: My skin was very severely affected by systemic sclerosis.

How much did your skin's tightness limit your daily activities in the last week?

- 0: skin tightness did not limit activity
- 1: skin tightness mildly limited my activity
- 2: skin tightness moderately limited my activity
- 3: skin tightness severely limited my activity
- 4: skin tightness very severely limited my activity

How has your skin 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

9.5.1.9.4 Scleroderma Health Assessment Questionnaire

The SHAQ consists of the HAQ-DI (8 domains) and also includes a VAS for pain and the following scleroderma-specific VASs: patient global assessment, vascular, digital ulcers, lung involvement and gastrointestinal involvement [Steen and Medsger, 1997]. Developers added the global questions to the HAQ-DI based on evaluation of SSc patients at the University of

Pittsburgh Scleroderma Clinic, their HAQ scores, patient report of symptoms and lab tests. The 5 scleroderma-specific VASs ask subjects how much symptoms interfere with daily activities and are scored similarly to a pain VAS. Each VAS score is reported individually. Studies have supported excellent test-retest reliability and construct validity (correlation with other measures in the direction and to the magnitude expected) and responsiveness of abatacept vs placebo for the global questions from the SHAQ [Johnson et al., 2005; Smyth et al., 2003; Khanna et al., 2020].

9.5.1.9.5 UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument

The UCLA SCTC GIT 2.0 captures SSc-related gastrointestinal activity and severity. This instrument is an improvement over the scleroderma gastrointestinal tract (SSC-GIT 1.0) instrument because it is shorter (34 items versus 52 items) but still reliable and valid instrument that differentiates reflux symptoms from symptoms of distension/bloating, adds a scale to evaluate rectal incontinence because of its high prevalence in SSc and develops a composite score that captures overall gastrointestinal tract burden associated with SSc [Khanna et al., 2009].

The UCLA SCTC GIT 2.0 has 7 scales—reflux, distension/bloating, diarrhea, fecal soilage, constipation, emotional well-being and social functioning; a total GIT score is also calculated to capture overall burden of SSc-associated gastrointestinal involvement. Items are scored on a 0 to 3 scale and do not require conversion to a 0 to 100 scale.

9.5.1.9.6 Raynaud's Assessment

The Raynaud's Condition Score Diary captures frequency, duration and severity of Raynaud's phenomenon activity and has face, content, criterion, discriminant and construct validity in subjects with SSc [Merkel et al., 2003]. Subjects will be provided an electronic device to capture symptoms.

9.5.1.10 Health Status and Systemic Sclerosis-specific Quality of Life Measures

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

9.5.1.10.1 Systemic Sclerosis Quality of Life Questionnaire

The SScQoL, developed through concept elicitation interviews in patients with diffuse cutaneous and limited cutaneous SSc, is a validated tool that has 29 questions divided into 5 subscales relating to physical functioning, emotional functioning, social functioning, sleep and pain, which are important disease-specific factors associated with quality of life in SSc [Sierakowska et al., 2019]. Good test-retest reliability and construct validity has been shown [Reay 2008]. No studies have yet determined responsiveness to date.

9.5.1.10.2 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 (PCS) and mental component score (MCS) 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.

9.5.1.10.3 Pain Questionnaire

Subjects will complete a pain questionnaire that has 3 questions regarding the severity of pain experienced during the past week due to Raynaud's, arthritis and finger ulceration and/or calcinosis. Subjects will rate their pain from 0 (no pain) to 10 (very severe pain).

9.5.1.10.4 Functional Assessment of Chronic Illness Therapy – Fatigue Scale

The FACIT-F is a 13-item measure that assesses self-reported fatigue and its impact upon daily activities and function. It was developed in the mid-1990s to meet a growing demand for more precise evaluation of fatigue associated with anemia in cancer patients. Subsequent to its development, it has been employed in over 150 published studies, including over 40,000 patients. Studied groups have included patients with cancer, rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, multiple sclerosis, psoriasis and SSc. The FACIT-F is reliable and valid in subjects with SSc [Harel et al., 2012; Strickland et al., 2012].

9.5.2 Pharmacokinetic Measurements

Blood samples will be collected from all subjects to evaluate the PK of fipaxalparant (HZN-825) at each of the following visits: Day 1 (pre-dose), Week 4 (pre-dose and 2 to 4 hours post-dose) and Weeks 16, 28 and 40 (pre-dose only at these 3 visits). For the Week 4 Visit (the only visit with post-dose PK samples), the morning dose regimen will be taken in the clinic. All pre-dose samples will be collected prior to any fipaxalparant (HZN-825) administration for the day. 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 (i.e., Day 1 and Weeks 4, 16, 28 and 40), subjects will be instructed to withhold taking fipaxalparant (HZN-825) before the visit, and fipaxalparant (HZN-825) and a meal will be administered in the clinic after the pre-dose PK samples are taken. Time of fipaxalparant (HZN-825) 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 Week 4 Visit.

If the clinic visit is in the afternoon, on days when a pre-dose PK sample will be collected (i.e., Day 1 and Weeks 4, 16, 28 and 40), subjects will be instructed to take fipaxalparant (HZN-825) before 8 a.m. with a meal and record dosing time; 1 PK sample will be

collected anytime during the clinic. For the Week 4 Visit, 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 and an additional PK sample will be collected 2 to 4 hours post-dose during this visit. At Weeks 16, 28 and 40, subjects will be instructed to take the evening dose at regular dosing time.

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.

9.5.3 Safety Variables

Safety will be assessed via AEs, concomitant medication use, physical examination, vital signs, [redacted] assessment, laboratory evaluations and 12-lead ECG.

9.5.3.1 Adverse Events

9.5.3.1.1 Definitions

9.5.3.1.1.1 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., SSc). 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.

9.5.3.1.1.2 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.

9.5.3.1.1.3 Non-serious Adverse Event Definition

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

9.5.3.1.1.4 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:

[redacted]

[redacted]

If any symptoms occur during the assessment in combination with the blood pressure reductions noted above, they are considered as part of the [redacted] 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 [redacted] will not be recorded.

Signs and symptoms associated with [redacted] 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.

9.5.3.1.2 Documentation of Adverse Events

AEs that are ongoing at the completion of HZNP-HZN-825-301 and/or occur prior to dosing on Day 1 will be considered pre-dose AEs. The TEAE reporting period begins with administration of the first dose of fipaxalparant (HZN-825) in this extension trial on Day 1 and continues until 4 weeks after the last dose of fipaxalparant (HZN-825) or premature discontinuation. All pre-dose AEs, TEAEs and AEs during the Follow-up Period must be recorded in the source documents and on the subject's eCRF. If a subject discontinues due to an SAE, that subject will be followed per Section 9.5.3.1.5.

If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by fipaxalparant (HZN-825), the Investigator will report this SAE using the procedures described in Section 9.5.3.1.5. 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 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.

9.5.3.1.3 Intensity or Severity of Adverse Events

All AEs, both serious and non-serious, will be assessed for severity using the Rheumatology Common Toxicity Criteria (RCTC) 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), fipaxalparant (HZN-825) continued
- Grade 3 (severe) – prolonged symptoms, reversible, major functional impairment, prescription medications/partial relief, hospitalized <24 hours, temporary fipaxalparant (HZN-825) discontinuation or/and dose reduced
- Grade 4 (includes life-threatening) – at risk of death, substantial disability, especially if permanent, hospitalized >24 hours, permanent fipaxalparant (HZN-825) discontinuation

9.5.3.1.4 Relationship or Causality to Fipaxalparant (HZN-825)

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 fipaxalparant (HZN-825) 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.

9.5.3.1.5 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 fipaxalparant (HZN-825) 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 fipaxalparant (HZN-825):

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 form **immediately and not later than 24 hours** after becoming aware that a subject has experienced an SAE.
   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

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.

9.5.3.1.5.1 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 fipaxalparant (HZN-825). These anticipated SAEs are provided in Section 17.13 (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.

9.5.3.1.6 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 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.

9.5.3.1.7 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 9.5.3.1.2 and 9.5.3.1.5, 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.

9.5.3.1.8 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 fipaxalparant (HZN-825), including periodic review and analyses of cumulative safety data for the trial.

9.5.3.1.9 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.

9.5.3.1.10 Development Safety Update Reports

The Sponsor will prepare and submit Development Safety Update Reports (DSUR) to all relevant regulatory authorities in countries and regions where the trial is conducted.

The Sponsor will prepare a single 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.

9.5.3.1.11 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.

9.5.3.1.12 Safety Monitoring Plan

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

9.5.3.2 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, urine pregnancy tests should also be done every 4 weeks after Day 1, which includes both in-clinic testing at scheduled visits prior to dosing [redacted] and at home (±7 day-window) by the subject and reported to the site [redacted] A urine pregnancy test will also be done at the Safety Follow-up Visit (whether at the clinic or at a remote site).

If a female subject becomes pregnant during the Treatment Period, she should immediately notify the Investigator and fipaxalparant (HZN-825) 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 fipaxalparant (HZN-825). Pregnancies occurring up to 4 weeks after the last dose of fipaxalparant (HZN-825) 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
- 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.

9.5.3.3 Vital Signs and Weight

Blood pressure 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 will be measured. To limit the potential for variability in weight collection, the subject should wear lightweight clothing and no shoes during weighing.

[redacted]

9.5.3.5 Physical Examination

A complete physical examination, including but not limited to cardiac, pulmonary, neurologic and skin assessments, as well as directed rheumatology assessments [redacted], will be performed.

9.5.3.6 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.

9.5.3.7 Echocardiogram

A standard transthoracic echocardiogram will be conducted on Day 1. However, an echocardiogram that has been performed during HZNP-HZN-825-301 and within the 3 months prior to HZNP-HZN-825-302 Day 1 can serve as the Trial Baseline echocardiogram if the subject has been clinically stable.

Additional echocardiograms will be conducted, if clinically indicated.

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.

9.5.3.8 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, glucose, phosphate, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase, uric acid, lactate dehydrogenase and liver function tests (ALT, AST, gamma glutamyltransferase, alkaline phosphatase, total bile acid, TBL, conjugated and unconjugated bilirubin, if applicable).

Lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides) will also be evaluated.

Subjects should be fasting for the Day 1, Week 28 and Week 52/Premature Discontinuation Visits.

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. [redacted]

Urinalysis parameters, including reflex testing if abnormal on dipstick, to be evaluated include urine glucose, protein, bilirubin, urobilinogen, pH, blood, ketone, nitrite, leukocyte esterase, appearance, specific gravity and color.

Samples for high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR) and autoantibodies (anti-centromere antibody, anti-RNA polymerase antibody, anti-topoisomerase 1 and anti-U1 small nuclear ribonucleoprotein) will also be collected.

Instructions for the collection, handling and analysis of clinical laboratory samples will be provided to the site prior to trial site initiation.

9.5.4 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 HAQ-DI [Cole et al., 2006], SHAQ [Johnson et al., 2005; Steen and Medsger, 1997], UCLA SCTC GIT 2.0 [Khanna et al., 2009], SSPRO-18 [Man et al., 2017], Raynaud's Condition Score Diary [Merkel et al., 2003], SScQoL [Sierakowska et al., 2019], SF-12 [Andrade et al., 2007; Khanna et al., 2010] and FACIT-F [Harel et al., 2012; Strickland et al., 2012] have been validated for use in subjects with SSc.

9.5.5 Trial Procedures

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

Select visits 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.

9.5.5.1 Effect of a Pandemic on Trial Procedures

In situations due to coronavirus disease 2019 (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 fipaxalparant (HZN-825) 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 Endpoints

Two types of Baseline are defined:

- Trial Baseline, defined as the latest measurement prior to the first dose of fipaxalparant (HZN-825) in this extension trial

- Fipaxalparant (HZN-825) Baseline, defined as the latest measurement prior to the first dose of the trial drug in Trial HZNP-HZN-825-301.

9.6.1.1 Primary Efficacy Endpoint

The primary endpoint is the change from both Baselines in FVC % predicted at Week 52.

9.6.1.2 Exploratory Efficacy Endpoints

1. Change from both Baselines in the mRSS at Week 52.
2. Proportion of subjects responding to treatment based on CRISS 25 at Week 52.
3. Change from both Baselines in HAQ-DI at Week 52.
4. Change from both Baselines in CGA at Week 52.
5. Change from both Baselines in PTGA at Week 52.
6. Change from both Baselines in the Physical Effects subscale of the SSPRO-18 at Week 52.
7. Change from both Baselines in the Physical Limitations subscale of the SSPRO-18 at Week 52.
8. Proportion of subjects with an mRSS decrease of ≥5 points and 25% from both Baselines at Week 52.
9. Responder rate (defined as ACR-CRISS [predicted probability] of at least 0.6) at Week 52.
10. Change from both Baselines in the SSPRO-18 at Week 52.
11. Change from both Baselines in each scale of the UCLA SCTC GIT 2.0 and the total GIT score at Week 52.
12. Change from both Baselines in Raynaud's phenomenon using the Raynaud's Assessment at Week 52.
13. Change from both Baselines in the SHAQ at Week 52.

14. Change from both Baselines in SScQoL scores at Week 52.
15. Change from both Baselines in SF-12 scores at Week 52.
16. Change from both Baselines in pain and pain component scale scores at Week 52.
17. Change from both Baselines in the FACIT-F score at Week 52.
18. Change from both Baselines in lung fibrosis based on HRCT at Week 52.
19. Change from both Baselines in DLCO at Week 52.
20. Change from both Baselines in serum and plasma biomarkers associated with $LPAR_1$ pathway, inflammation and/or fibrosis at [redacted]
21. Change from both Baselines in [redacted]

9.6.1.3 Safety and Tolerability Endpoints

1. Incidence of TEAEs and the AESI [redacted]
2. Concomitant medication use.
3. Vital signs.
4. 12-lead ECGs.
5. Clinical safety laboratory evaluations.

9.6.1.4 Pharmacokinetic Endpoint

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

9.6.2 Analysis Sets

Four analysis sets will be defined for this trial.

- The full analysis set (FAS) will include all subjects who were enrolled (i.e., signed the ICF) and who received at least 1 dose or partial dose of fipaxalparant (HZN-825) in this extension trial. This will be the analysis set used for efficacy data analyses and subjects will be analyzed according to the treatment group to which they were randomized in the previous trial, and combined into an 'overall' group.
- The safety analysis set will include all subjects who received at least 1 dose or partial dose of fipaxalparant (HZN-825) in this extension trial. Subjects in this analysis set will be analyzed according to the group determined by the treatment that the subject received in the previous trial and overall, 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 had at least 1 PK sample post fipaxalparant (HZN-825) treatment in this extension trial.
- The Per-Protocol (PP) analysis set will consist of all subjects in the FAS with no major protocol violations. The PP analysis set will be used, as needed, for supportive analysis of the primary endpoint and potentially other key endpoints. Subjects in this analysis set

will be analyzed according to the treatment group to which they were randomized in the previous trial, and combined into an 'overall' group.

9.6.3 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 HZNP-HZN-825-301 and overall.

A mixed model for repeated measures (MMRM) will be fit to the data *for descriptive purposes* using observed change in FVC % predicted values from all planned post-Trial Baseline assessments (Weeks 16, 28, 40 and 52). The model will include the fixed covariates of: factors used for stratifying randomization (use of mycophenolate mofetil [yes/no] and presence of ILD [yes/no]), treatment the subject received in the previous trial, treatment by Visit Week and Visit Week. The Trial Baseline value will be used as a continuous covariate. 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 Trial 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.

9.6.4 Safety and Tolerability Analyses

All safety endpoints will be summarized 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) for each unique System Organ Class 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 fipaxalparant (HZN-825), as assessed by the Investigator. Grade 3 and above TEAEs will also be summarized for each unique System Organ Class and Preferred Term. AESIs will be summarized.

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 Trial 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 open-label extension 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 Trial Baseline and fipaxalparant (HZN-825) Baseline will be presented for each vital sign parameter by visit. A shift table for vital signs by toxicity grade and visit will be summarized.

9.6.5 Pharmacokinetic Analyses

PK data will be analyzed using the PK analysis set. Plasma concentrations of fipaxalparant (HZN-825) and metabolite(s) (if applicable) 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 HZNP-HZN-825-301 and by time point. Population PK analysis may be performed.

9.6.6 Autoantibody Analyses

The presence of anti-centromere antibody, anti-RNA polymerase antibody, anti-topoisomerase 1 and anti-U1 small nuclear ribonucleoprotein will be evaluated.

9.6.7 Interim Analyses

No interim analyses are planned.

9.6.8 Sample Size and Power Considerations

The sample size is based on the number of subjects who completed Trial HZNP-HZN-825-301.

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 IRB/IEC.

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 IRB/IEC 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 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 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 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 US 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:

- Good Clinical Practice (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, IRB/IEC 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.

Andrade TL, Camelier AA, Rosa FW, et al. Applicability of the 12-Item Short-Form Health Survey in patients with progressive systemic sclerosis. J Bras Pneumol. 2007;33:414-22.

Asano Y. Recent advances in the treatment of skin involvement in systemic sclerosis. Inflamm Regen. 2017;37:12.

Asano Y, Sato S. Vasculopathy in scleroderma. Semin Immunopathol. 2015;37(5):489-500.

Bhattacharyya S, Wei J, Varga J. Understanding fibrosis in systemic sclerosis: shifting paradigms, emerging opportunities. Nat Rev Rheumatol. 2011;8(1):42-54.

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.

Cole JC, Khanna D, Clements PJ, et al. Single-factor scoring validation for the Health Assessment Questionnaire-Disability Index (HAQ-DI) in patients with systemic sclerosis and comparison with early rheumatoid arthritis patients. Qual Life Res. 2006;15(8):1383-94.

Del Galdo F, Hartley C, Allanore Y. Randomised controlled trials in systemic sclerosis: patient selection and endpoints for next generation trials. Lancet Rheumatol. 2020:e173-84.

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.

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.

Harel D, Thombs BD, Hudson M, Baron M, Steele R, Canadian Scleroderma Research Group. Measuring fatigue in SSc: a comparison of the Short Form-36 Vitality subscale and Functional Assessment of Chronic Illness Therapy-Fatigue scale. Rheumatology (Oxford). 2012:51:2177-85.

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

Johnson SR, Hawker GA, Davis AM. The Health Assessment Questionnaire Disability Index and Scleroderma Health Assessment Questionnaire in scleroderma trials: an evaluation of their measurement properties. Arthritis Rheum. 2005;53:256-62.

Khanna D, Berrocal VJ, Giannini EH, et al. The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. Arthritis Rheumatol. 2016;68(2):299-311.

Khanna D, Frech T, Khanna PP, et al. Valuation of scleroderma and psoriatic arthritis health states by the general public. Health Qual Life Outcomes. 2010;8:112.

Khanna D, Furst DE, Clements PJ, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017;2(1):11-8.

Khanna D, Hays RD, Maranian P, et al. Reliability and validity of UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) instrument. Arthritis Rheumatol. 2009;61(9):1257-63.

Khanna D, Spino C, Johnson S, et al. Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase 2 investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial. Arthritis Rheumatol. 2020;72:125-36.

Ledein L, Léger B, Dees C, et al. Translational engagement of lysophosphatidic acid receptor 1 in skin fibrosis: from dermal fibroblasts of patients with scleroderma to tight skin 1 mouse. Br J Pharmacol. 2020;177(18):4296-309.

Man A, Correa JK, Ziemek J, Simms RW, Felson DT, Lafyatis R. Development and validation of a patient-reported outcome instrument for skin involvement in patients with systemic sclerosis. Ann Rheum Dis. 2017;76:1374-80.

Mayes M, Lacey J Jr, Beebe-Dimmer J, et al. Prevalence, incidence, survival and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum. 2003;48(8):2246–55.

Merkel PA, Clements PJ, Reveille JD, et al. Current status of outcome measure development for clinical trials in systemic sclerosis. Report from OMERACT 6. J Rheumatol. 2003;30:1630-47.

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

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.

Pope JE. The future of treatment in systemic sclerosis: can we design better trials? Lancet Rheumatol. 2020:e185-94.

Pradère JP, Klein J, Grès S, et al. LPA_1 receptor activation promotes renal interstitial fibrosis. J Am Soc Nephrol. 2007;18(12):3110-8.

Reay N. The quality of life in patients with diffuse and limited systemic sclerosis. Published online 2008. https://etheses.whiterose.ac.uk/26111/1/503274.pdf.

Sierakowska M, Doroszkiewicz H, Sierakowska J, et al. Factors associated with quality of life in systemic sclerosis: a cross-sectional study. Qual Life Res. 2019;28:3347-54.

Smyth A, MacGregor A, Mukerjee D, Brough G, Black C, Denton C. A cross-sectional comparison of three self-reported functional indices in scleroderma. Rheumatology. 2003;42(6):732-8.

Spiera R, Hummers L, Chung L, et al. Safety and efficacy of lenabasum in a Phase II, randomized, placebo-controlled trial in adults with systemic sclerosis. Arthritis Rheumatol. 2020;72(8):1350-60.

Steen VD, Mayes MD, Merkel PA. Assessment of kidney involvement. Clin Exp Rheumatol. 2003;21(3Suppl29):S29-31.

Steen VD, Medsger TA Jr. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum. 1997;40:1984-91.

Strickland G, Pauling J, Cavill C, McHugh N. Predictors of health-related quality of life and fatigue in systemic sclerosis: evaluation of the EuroQol-5D and FACIT-F assessment tools. Clin Rheumatol. 2012;31:1215-22.

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.

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.

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

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

Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest. 2007;117(3):557-67.

Volkmann E, Varga J. Emerging targets of disease-modifying therapy for systemic sclerosis. Nat Rev Rheumatol. 2019;15(4):208-24.

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.

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 IRB/IEC must be notified of changes that are made to this section, but IRB/IEC 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], MD Medical Director Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015 Business 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]
Sponsor Contact for Serious Adverse Event Reporting	Horizon Therapeutics U.S.A., Inc. US Fax: 1-888-814-8653 (toll free, within USA) Ex US Fax: +44 (0)207-136-1046 Email (worldwide): svc-ags-in-us@amgen.com

17.2 Clinician Global Assessment (CGA)

Physician Global Assessment

A1. Subject ID #:_____-_____ A2. Visit Date:_____/_____/ 20_____
Month Day Year

Was this assessment completed by the physician? Yes ☐ No ☐

SECTION B: PHYSICIAN GLOBAL ASSESSMENT

B1. On a scale of 0-10, how was your patient's overall health in the LAST WEEK? **(Check one)**

Excellent — Extremely poor — Not known

0. ☐ 1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ 10. ☐ ☐

SECTION C: SCLERODERMA-RELATED HEALTH TRANSITION BY PHYSCIAN

C1. Compared to the LAST CLINICAL VISIT, how do you rate your patient's overall scleroderma? **(Check One)**

1. ☐ Much better
2. ☐ A little better
3. ☐ No change
4. ☐ A little worse
5. ☐ Much worse

Investigator Signature: _____

8/20/2017 Page 1 of 1

17.3 Modified Rodnan Skin Score (mRSS)

Modified Rodnan Skin Score

A1. Subject ID #: ___ ___ ___- ___ ___ ___ ___ A2. Visit Date: ___ ___ / ___ ___ / 20 ___ ___ (Month / Day / Year) A3. Staff Initials: ___ ___ ___

It is essential to have the same examiner for each patient throughout the study.

SECTION B: mRSS 88. ☐ Exam not done

Indicate the skin thickening score in the tables below by checking the box next to the score, for each of the 17 areas.

0 = normal, 1=MILD thickening, 2=MODERATE thickening, 3=SEVERE thickening

B1. Upper Extremities

	RIGHT				LEFT			
Fingers	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3
Hand	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3
Forearm	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3
Upper arm	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3

*If any of the Upper Extremities were not able to be scored, please indicate location and reason why:_____

B2. Torso

Face	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3
Chest	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3
Abdomen	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3

B3. Lower Extremities

	RIGHT				LEFT			
Thigh	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3
Leg	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3
Foot	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3	0. ☐ 0	1. ☐ 1	2. ☐ 2	3. ☐ 3

*If any of the Lower Extremities were not able to be scored, please indicate location and reason why:_____

_____

_____

B4. Sum the 17 area scores for the Total mRSS score: ☐☐

Assessors Signature: _____

Source: Khanna et al., 2017

17.4 Scleroderma Health Assessment Questionnaire (SHAQ)

HEALTH ASSESSMENT QUESTIONNAIRE

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add comments.

Please check the one response that best describes your usual abilities
IN THE PAST SEVEN DAYS:

	Without **ANY** difficulty	With **SOME** difficulty	With **MUCH** difficulty	**UNABLE** to do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons	____	____	____	____
- Shampoo your hair?	____	____	____	____
ARISING				
Are you able to :				
- Stand up from an armless straight chair?	____	____	____	____
- Get in and out of bed?	____	____	____	____
EATING				
Are you able to:				
- Cut your meat?	____	____	____	____
- Lift a full glass to your mouth?	____	____	____	____
- Open a new milk carton?	____	____	____	____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	____	____	____	____
- Climb up five stairs?	____	____	____	____

Please check any **AIDS or DEVICES** that you usually use for any of these activities:

____ Cane
____ Walker
____ Crutches
____ Wheelchair
____ Devices for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
____ Built up or special utensils
____ Special or built-up chair
____ Other (specify: _____)

Please check any categories for which you usually need **ASSISTANCE FROM ANOTHER PERSON:**

____ Dressing and grooming
____ Arising
____ Eating
____ Walking

SHAQ – United States/English - Mapi.
SHAQ_AU2.0_eng-USori.doc

HEALTH ASSESSMENT QUESTIONNAIRE, cont.

Please check the one response which best describes your usual abilities **IN THE THE PAST SEVEN DAYS:**

	Without **ANY** difficulty	With **SOME** difficulty	With **MUCH** difficulty	**UNABLE** to do
HYGIENE				
Are you able to:				
- Wash and dry your entire body?	____	____	____	____
- Take a tub bath?	____	____	____	____
- Get on and off the toilet?	____	____	____	____
REACH				
Are you able to :				
- Reach and get down a 5 pound object (such as a bag of sugar) from just over your head?	____	____	____	____
- Bend down and pick up clothing off the floor?	____	____	____	____
GRIP				
Are you able to:				
- Open car doors?	____	____	____	____
- Open jars that have been previously opened?	____	____	____	____
- Turn faucets on and off?	____	____	____	____
ACTIVITIES				
Are you able to:				
- Run errands and shop?	____	____	____	____
- Get in and out of a car?	____	____	____	____
- Do chores such as vacuuming or yardwork?	____	____	____	____

Please check any **AIDS** or **DEVICES** that you usually use for any of these activities:

_____ Raised Toilet Seats _____ Bathtub Bar _____ Bathtub Seat
_____ Long-Handled Appliances for Reach _____ Jar Opener (for jars previously opened)
_____ Long-Handled Appliances in Bathroom Other (specify: _____)

Please check any categories for which you usually need **HELP FROM ANOTHER PERSON**:

_____ Hygiene _____ Gripping and Opening Things
_____ Reach _____ Errands and Chores

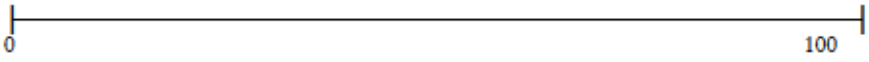
SHAQ – United States/English - Mapi.
SHAQ_AU2.0_eng-USori.doc

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness **IN THE PAST WEEK ?**

PLACE A MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

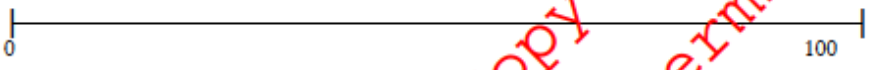
NO PAIN — VERY SEVERE PAIN



IN THE PAST WEEK, how much have your intestinal problems interfered with your daily activities?

PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

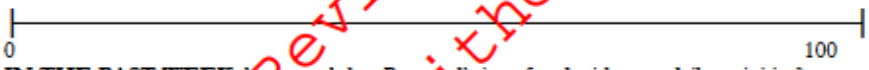
INTESTINAL PROBLEMS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION



IN THE PAST WEEK, how much have your breathing problems interfered with your daily activities?

PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

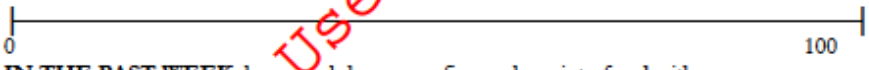
BREATHING PROBLEMS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION



IN THE PAST WEEK, how much has Raynaud's interfered with your daily activities?

PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

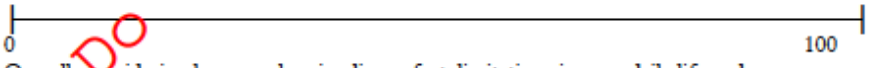
RAYNAUD'S DOES NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION



IN THE PAST WEEK, how much have your finger ulcers interfered with your daily activities?

PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

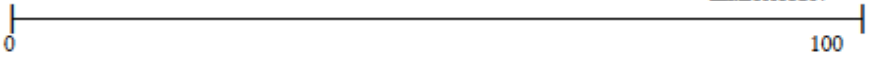
FINGER ULCERS DO NOT LIMIT ACTIVITIES — VERY SEVERE LIMITATION



Overall, considering how much pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your disease today?

PLACE A MARK ON THE LINE TO INDICATE THE LIMITATION OF ACTIVITY.

NO DISEASE — VERY SEVERE LIMITATION



Steen VD, Medgers TA. The Value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum 1997 Nov ; 40 (11):1984–1991.
SHAQ – United States/English - Mapi.
SHAQ_AU2.0_eng-USori.doc

17.5 Patient Global Assessment (PTGA)

Patient Global Assessment

A1. On a scale of 0-10, how was your overall health in the LAST WEEK? **(Check one)**

Excellent 0. ☐ 1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ Extremely poor 10. ☐

B1. Compared to your LAST VISIT, how do you rate your overall "scleroderma" skin involvement? **(Check One)**

1. ☐ Much better
2. ☐ A little better
3. ☐ No change
4. ☐ A little worse
5. ☐ Much worse

C1. On a scale of 0-10, how much pain have you had because of your illness in the LAST WEEK? **(Check One)**

No pain 0. ☐ 1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ Severe pain 10. ☐

D1. On a scale of 0-10, in the LAST MONTH how much has your skin involvement due to your scleroderma interfered with your daily activity? **(Check One)**

Did not limit activity 0. ☐ 1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ Very severe limitation 10. ☐

D2. We also want to assess how active your skin involvement is. By active we mean how rapidly your skin disease has been progressing. On a scale of 0-10, in the LAST MONTH how active has your skin involvement been? **(Check One)**

Not active 0. ☐ 1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐ 8. ☐ 9. ☐ Extremely active 10. ☐

17.6 Scleroderma Skin Patient-reported Outcome (SSPRO-18)

SCLERODERMA SKIN PATIENT REPORTED OUTCOME (SSPRO)

Page 1 of 2

We would like to know how scleroderma affects your SKIN and how these skin problems have affected the way you feel and do things. Please try to think back to your SKIN as you answer these questions.

Note that ulcers on your hands or fingers or Raynaud's symptoms are NOT the focus of this questionnaire, as they are more related to how scleroderma affects the blood vessels.

Some questions may have different meanings for different people, please answer according to whatever you feel the question means for you.

Over the PAST 4 WEEKS:	Not at all → Very Much
1. How tight has your skin felt?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
2. How dry has your skin been?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
3. How painful has your skin been?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
4. How discolored has your skin been?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
5. How itchy has your skin felt?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
6. How self-conscious have you been because of your skin?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
7. How worried have you been about your skin?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
8. How depressed have you been about your skin?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
9. How much have you not felt like your true self because of the way your skin is?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
10. How frustrated have you been about your skin?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
11. How much have you felt like you lack control over your skin's condition?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6

Version: November 2017

SCLERODERMA SKIN PATIENT REPORTED OUTCOME (SSPRO)

12. How much difficulty have you had **doing things with your hands** because of skin tightness?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
13. How much difficulty have you had with **opening or closing your mouth** because of skin tightness?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
14. How much difficulty have you had with **moving parts of your body** because of skin tightness?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
15. How much has your skin's condition interfered with your **daily activities** (examples: work, study, leisure activities)?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
16. How much has your skin **prevented you from going out to socialize?**	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
17. How much has your skin interfered with your **interactions with people?**	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
18. How much has your skin affected the **clothes** you wear?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6

Version: November 2017

17.7 University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) Instrument

ID: _____ Date: _____

The following questions ask about your gastrointestinal (gut, GI) symptoms and how they affected your life over the last 7 days. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

		In the past 1 week, how often did you	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]	
REFLUX	1.	… have difficulty swallowing solid food?	☐	☐	☐	☐	1/8= 0.125 2/8= 0.25 3/8= 0.375 4/8= 0.5 5/8= 0.625 6/8= 0.75 7/8= 0.875 8/8= 1.0 9/8= 1.125 10/8= 1.25 11/8= 1.375 12/8= 1.5 13/8= 1.625 14/8= 1.75 15/8= 1.875 16/8= 2.0 17/8= 2.125 18/8= 2.25 19/8= 2.375 20/8= 2.5 21/8= 2.625 22/8= 2.75 23/8= 2.875 24/8= 3.0 SCORE R=
	2.	… have an unpleasant stinging or burning sensation in your chest (heartburn)?	☐	☐	☐	☐	
	3.	… have a sensation of bitter or sour fluid coming up from your stomach into your mouth (acid reflux)?	☐	☐	☐	☐	
	4.	… have heartburn on eating 'acidic' foods such as Tomatoes & Oranges?	☐	☐	☐	☐	
	5.	… regurgitate (throw up or bring up small amounts of previously eaten food)?	☐	☐	☐	☐	
	6.	… sleep in a 'raised' or an 'L shaped' position?	☐	☐	☐	☐	
	7.	… feel like vomiting or throwing up?	☐	☐	☐	☐	
	8.	… vomit or throw up?	☐	☐	☐	☐	
DISTENSION	9.	… feel bloated (a sensation of gas or air in the stomach)?	☐	☐	☐	☐	1/4= 0.25 2/4= 0.5 3/4= 0.75 4/4= 1.0 5/4= 1.25 6/4= 1.5 7/4= 1.75 8/4= 2.0 9/4= 2.25 10/4= 2.5 11/4= 2.75 12/4=3.0 SCORE D/B=
	10.	… notice an increase in your belly, sometimes requiring you to open your belt, pants or shirt?	☐	☐	☐	☐	
	11.	… feel full after eating a small meal?	☐	☐	☐	☐	
	12.	… pass excessive gas or flatulence?	☐	☐	☐	☐	
SOILAGE	13.	… accidentally soil (dirty) your underwear before being able to get to a bathroom?	☐	☐	☐	☐	1/1= 1.0 2/1= 2.0 3/1= 3.0 SCORE S=

© [redacted] MD, MSc 2 UCLA SCTC GIT 2.0
English for USA

DIARRHEA

In the past 1 week, how often did you		(CHECK ONE RESPONSE FOR EACH QUESTION)			
		No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
14.	… have loose stools (diarrhea)?	☐	☐	☐	☐

In the past 1 week, have you noticed your stools becoming		(CHECK ONE RESPONSE FOR EACH QUESTION)	
		Yes[1]	No[0]
15.	… watery?	☐	☐

1/2= 0.5
2/2= 1.0
3/2= 1.5
4/2= 2.0

SCORE D=

SOCIAL FUNCTIONING

In the past 1 week, how often did the following interfere with social activities (such as visiting friends or relatives)?		(CHECK ONE RESPONSE FOR EACH QUESTION)			
		No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
16.	… Nausea	☐	☐	☐	☐
17.	… Vomiting	☐	☐	☐	☐
18.	… Stomach ache or pain	☐	☐	☐	☐
19.	… Diarrhea	☐	☐	☐	☐
20.	… Worry you would accidentally soil your underwear	☐	☐	☐	☐
21.	… Bloated sensation	☐	☐	☐	☐

1/6= 0.16
2/6= 0.33
3/6= 0.5
4/6= 0.66
5/6= 0.83
6/6= 1.0
7/6= 1.16
8/6= 1.33
9/6= 1.5
10/6= 1.66
11/6= 1.83
12/6= 2.0
13/6= 2.16
14/6= 2.33
15/6= 2.5
16/6= 2.66
17/6= 2.83
18/6= 3.0

SCORE SF=

		In the past 1 week, how often did you	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]	
EMOTIONAL WELLBEING	22.	… feel worried or anxious about your bowel problems?	☐	☐	☐	☐	1/9= 0.11 2/9= 0.22 3/9= 0.33 4/9= 0.44 5/9= 0.55 6/9= 0.66 7/9= 0.77 8/9= 0.88 9/9= 1.0 10/9= 1.11 11/9= 1.22 12/9= 1.33 13/9= 1.44 14/9= 1.55 15/9= 1.66 16/9= 1.77 17/9= 1.88 18/9= 2.00 19/9= 2.11 20/9= 2.22 21/9= 2.33 22/9= 2.44 23/9= 2.55 24/9= 2.66 25/9= 2.77 26/9= 2.88 27/9= 3.0 SCORE EWB=
	23.	… feel embarrassed because of your bowel symptoms?	☐	☐	☐	☐	
	24.	… have problems with sexual relations because of your bowel symptoms?	☐	☐	☐	☐	
	25.	… fear not finding a bathroom?	☐	☐	☐	☐	
	26.	… feel depressed or discouraged due to your bowel symptoms?	☐	☐	☐	☐	
	27.	… avoid or delay traveling because of your bowel symptoms?	☐	☐	☐	☐	
	28.	… feel angry or frustrated as a result of your bowel symptoms?	☐	☐	☐	☐	
	29.	… have problems with your sleep as a result of your bowel symptoms?	☐	☐	☐	☐	
	30.	… feel 'stress' or an upset mood worsens your bowel symptoms?	☐	☐	☐	☐	

CONSTIPATION

	In the past 1 week, have you noticed your stools becoming	(CHECK ONE RESPONSE FOR EACH QUESTION) Yes[1]	No[0]
31.	… harder?	☐	☐

	In the past 1 week, how often	(CHECK ONE RESPONSE FOR EACH QUESTION) No Days[0]	1-2 Days[1]	3-4 Days[2]	5-7 Days[3]
32.	… were you constipated or unable to empty your bowels?	☐	☐	☐	☐
33.	… did you have hard stools?	☐	☐	☐	☐
34.	… did you have pain while passing your stools?	☐	☐	☐	☐

1/4= 0.25
2/4= 0.50
3/4= 0.75
4/4= 1.0
5/4= 1.25
6/4= 1.50
7/4= 1.75
8/4= 2.0
9/4= 2.25
10/4= 2.5

SCORE C=

Thank you for completing the questionnaire

To be completed by the physician

TOTAL SCORE= + Reflux _____
+ Distention /Bloating _____
+ Fecal Soilage _____
+ Diarrhea _____
+ Social functioning _____
+ Emotional well-being _____
TOTAL SCORE= (_____) /6= _____

REMEMBER: CONSTIPATION SCORE IS NOT INCLUDED IN CALCULATION OF TOTAL SCORE

C=Constipation; D=Diarrhea; D/B=Distention/Bloating; EWB=Emotional well-being; R=Reflux; SF=Social functioning; S=Fecal soilage

17.8 Raynaud's Assessment

Raynaud's Assessment (daily on handheld)

Pick the number that best indicates the difficulty you had today with your Raynaud's condition:

0	1	2	3	4	5	6	7	8	9	10
No Difficulty										Extreme Difficulty

How many Raynaud's attacks have you had today?

How many minutes did the longest attack last?

17.9 Systemic Sclerosis Quality of Life Questionnaire (SScQoL)

SSc-QoL

Date:

Name:_____ Age: _____ Sex:_____

On the following pages you will find some statements which have been made by people who have suffered with Scleroderma

Instructions: This questionnaire consists of 29 statements. Please read each statement carefully, and then choose **True** if the statement applies to you and choose **Not True** if it does not apply to you **at the moment.** Circle the appropriate number.

1. **I can't do anything without really thinking it through**
   1 True
   0 Not True

2. **It's always on my mind**
   1 True
   0 Not True

3. **I worry that I let people down**
   1 True
   0 Not True

4. **My condition makes me angry**
   1 True
   0 Not True

5. **I would like to be spontaneous**
   1 True
   0 Not True

6. **I get upset when I can't do things**
   1 True
   0 Not True

7. **I often get frustrated**
   1 True
   0 Not True

8. **I cannot rely on how I will be tomorrow**
   1 True
   0 Not True

9. **My condition means I have disturbed sleep**
   1 True
   0 Not True

10. **It has affected me a lot socially**
    1 True
    0 Not True

11. **It has affected the health of people around me**
    1 True
    0 Not True

12. **My hands don't work as well as they did**
    1 True
    0 Not True

13. **It puts a strain on my personal relationships**
    1 True
    0 Not True

Continue on Back

14. I need to rest more often 1 True 0 Not True	22. Household tasks can be a problem 1 True 0 Not True
15. I avoid certain social situations because I am embarrassed 1 True 0 Not True	23. I have had to stop some of my hobbies 1 True 0 Not True
16. I find it difficult to take care of the people I'm close to 1 True 0 Not True	24. There are days when you are really tired and don't want to talk to anyone 1 True 0 Not True
17. I take to heart things which wouldn't have worried me before 1 True 0 Not True	25. I feel guilty at being ill 1 True 0 Not True
18. Life is just not what it was 1 True 0 Not True	26. I struggle to wash myself as I would like 1 True 0 Not True
19. I can't cope at all 1 True 0 Not True	27. I feel helpless 1 True 0 Not True
20. I feel very isolated 1 True 0 Not True	28. Pain tires me out 1 True 0 Not True
21. I am unable to join in activities with friends and family 1 True 0 Not True	29. I miss being able to sort things out 1 True 0 Not True

17.10 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.)?	○	○	○	○	○

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-1 of 1-

17.11 Pain Questionnaire

For each item, pick the number that represents the severity of your pain.

How much pain did you have in your hands when they were exposed to anything cold over the past one week?

0	1	2	3	4	5	6	7	8	9	10
No Pain										The Worst Pain Imaginable

How much pain did you have in your joints over the past one week?

0	1	2	3	4	5	6	7	8	9	10
No Pain										The Worst Pain Imaginable

How much pain did you have in your finger tip sores over the past one week, if applicable?

0	1	2	3	4	5	6	7	8	9	10
No Pain OR Not applicable										The Worst Pain Imaginable

17.12 Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F)

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

17.13 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 9.5.3.1.1.2 (Serious Adverse Event Definition). The Investigator is required to follow the requirements detailed in Section 9.5.3.1.5 (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 fipaxalparant (HZN-825) compared to events without fipaxalparant (HZN-825), an expedited IND safety report may be submitted to the FDA.

Renal system: scleroderma renal crisis (refer to Section 9.5.1.1 for the definition), accelerated hypertension

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, forced vital capacity decreased, interstitial lung disease

Gastrointestinal system: nausea, vomiting, diarrhea, intestinal pseudo-obstruction, malnutrition, abnormal loss of weight

Skin and subcutaneous system: skin ulcer, gangrene, extremity necrosis

[redacted]

HZNP-HZN-825-302 [redacted]

[redacted]

Version 3.0, Dated 14 June 2023 Page 1 of 3

[redacted]

References

[redacted]

17.15 Detailed Requirements for the Evaluation of Patients Detected with Abnormal Liver Function Test

Per protocol Section 9.3.3.1, 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.

An increase of serum aminotransferases to >3 × ULN and/or TBL >2 × ULN should be followed by repeat testing (ALT, AST, alkaline phosphatase, and TBL at minimum) within 48 to 72 hours to confirm the abnormality*.

A confirmed ALT/AST >3 × ULN and/or TBL >2 × ULN should be considered to record as AE. Please reach out to the Medical Monitor via Electronic Protocol Inquiry Platform to inform such events.

It is critical to exclude the other possible causes of increased liver enzymes. If needed, please consider hepatologist/gastroenterologist consultation early in the evaluation. Additional imaging and laboratory tests (e.g., abdominal ultrasound, Hepatitis panel testing, etc.), as deemed necessary, should be performed to ascertain the etiology.

Below are the requirements which need to be followed to ensure the close observation of patients who have confirmed ALT or AST levels >3 × ULN and/or TBL >2 × ULN:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

*If it is difficult for the subjects to return to the trial site promptly, the repeat test can be analyzed locally, but normal laboratory ranges should be recorded. Results should be made available to trial Investigators immediately and the data should be included in the case report forms.

The subject should return to the site for the lab testing as soon as possible.

Approval Signatures

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SUMMARY OF CHANGES
Protocol HZNP-HZN-825-302
Protocol Version 2.0, Amendment 1 (19 October 2022) to
Protocol Version 3.0, Amendment 2 (14 October 2024)

Key additions, revisions and clarifications to Version 3.0 of the protocol are:

- Updating to align with new company structure under new sponsor throughout.
- 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.
- Amending the order and content of the exploratory objectives to align with updates in the HZN-825-301 study objectives with a goal of enhancing the ability to demonstrate overall improvement in the disease. Additionally, to adapt to new updates in the definition of Revised Composite Response Index in Systemic Sclerosis (CRISS 25).
- Clarifying that trial drug must not begin until the subject is completely done with the HZN-825-301 study.
- Updating Physician Global Assessment to Clinician Global Assessment throughout the document to align with industry standards.
- Updating numbers referring to safety and efficacy data to that from most recently completed studies.
- Amending description of risks to align with current available data on risks associated with use of the investigational product.
- Updating manufacturer list to include [redacted]
- Introducing the revised CRISS (CRISS 25) into the endpoints and associated definitions to align throughout the protocol.
- Updating language to ensure subject safety and confidentiality if medical records need to be shared.
- 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 (SAE) and Outcomes for reported adverse events (AEs)/SAEs/adverse events of special interest (AESIs) to align protocol information with revised Clinical SAE Report Form/case report forms (CRFs).
- Other editorial, administrative, or alignment updates were made for consistency with the HZN-825-301 study.

SUMMARY OF CHANGES
Protocol HZNP-HZN-825-301
Version 2.0 Amendment 1, incorporating Protocol Version 1.0 and Administrative Change 1

Key additions, revisions and clarifications to Version 1.0 of the protocol are:

- Updating the Sponsor's address.
- Adding an ex-United States (US) fax number for emergency contact/serious adverse event reporting.
- Changing the signatory trial statistician.
- Clarifying the primary safety objective.
- Adding an exploratory objective and endpoint regarding evaluation of rheumatologic assessments and specifying what these assessments are [redacted]
- Adding new requirements around condom use and aligning text with Section 9.5.3.2 in exclusion criterion 3.
- Allowing subject visits to be performed at locations other than the trial site and adding clarity as to which visits are eligible to be performed at an alternate site location.
- Updating the protocol with information from the current Investigator's Brochure (Version 8) with respect to clinical experience with HZN-825 and rationale for this trial.
- Including information on the potential benefits of HZN-825 in the benefit/risk assessment section.
- 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 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.

- Stressing the importance of compliance with trial drug.
- Clarifying language for obtaining diffusing capacity of the lungs for carbon monoxide (DLCO) measurement.
- 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.
- Clarifying documentation and reporting for medication errors.
- Adding clarification around abstinence as a contraceptive method.
- Alerting trial personnel that the actual assessment instruments used may differ from those in Section 17 of the protocol.
- Updating the SF-12® Health Survey to the most current version.
- Updating the [redacted] Manual and protocol language to align the process of assessing [redacted] with current guidelines, to clarify the manual to make the process more understandable and improve the method of data collection for [redacted]
- Specifying that a repeat resting ECG should be conducted if a clinically significant ECG result is obtained.
- Specifying the urinalysis parameters.
- Making changes for consistency with the schedule of assessments.

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