CLINICAL TRIAL PROTOCOL FOR FIPAXALPARANT (HZN-825)

Protocol Number: HZNP-HZN-825-301
IND: 112818
EU CT Number: 2023-509782-20-00

A Randomized, Double-blind, Placebo-controlled, Repeat-dose, Multicenter Trial to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of HZN-825 in Patients with Diffuse Cutaneous Systemic Sclerosis

Date: 22 August 2024

Version 5.0

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

PROTOCOL

1 TITLE PAGE

Trial Title:	A Randomized, Double-blind, Placebo-controlled, Repeat-dose, Multicenter Trial to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of HZN-825 in Patients with Diffuse Cutaneous Systemic Sclerosis
Protocol Number:	HZNP-HZN-825-301
Version:	5.0
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:	22 August 2024

CONTACT IN THE EVENT OF AN EMERGENCY

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

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

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-HZN-825-301

Version: 5.0

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Version Date: 22 August 2024

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

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

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

Signature:

_____ _____

Name Date
Trial Center
Address
City State Country

SUMMARY OF CHANGES
Protocol Version 4.0, Amendment 3 (22 June 2023) to
Protocol Version 5.0, Amendment 4 (22 August 2024)

Key additions, revisions and clarifications to Version 5.0 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 secondary objectives to enhance 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 when all assessments must be completed to ensure study completion before subsequent treatment if joining another study.
- Amending language to clarify that unblinded dose selection is no longer applicable and other changed blinding activities.
- Clarifying that Exclusion criteria 21 only applies to the first 110 subjects.
- Updating Physician Global Assessment to Clinician Global Assessment throughout the document to align with industry standards.
- Removing language for a separate shift table to evaluate glucose as this is no longer applicable to the study.
- 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.
- Introducing the revised CRISS (CRISS 25) into the endpoints and associated definitions to align throughout the protocol.
- Adjusting language surrounding exit interviews and number of subjects participating in the interviews and align with CRISS 25.
- 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.
- Amending statistical language to align with changes in unblinding, simplify descriptions of analyses to be performed, and clarify that the independent data monitoring committee (IDMC) will review futility data.
- Updating principal investigator (PI) responsibilities to report serious breaches.

- Including definition of serious adverse events (SAE) 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).

SUMMARY TABLE OF CHANGES
Protocol Version 4.0 (22 June 2023) to
Protocol Version 5.0, Amendment 4 (22 August 2024)

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
Global HZN-825	**Global** fipaxalparant (HZN-825)	*To incorporate non-proprietary name throughout document*
Cover Page **EudraCT Number: 2020-005764-62**	**Cover Page** **EU CT Number: 2023-509782-20-00**	*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:**	**Title Page** **Sponsor's Responsible Medical Officer:**	*To change the Sponsor's approver with shift to Amgen processes*
Title Page - Contact in the event of an emergency Any death, life-threatening event or other serious adverse event experienced by a subject during the course of the trial, whether or not judged drug-related, must be reported immediately, without undue delay, but not later than 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF).	**Title Page - Contact in the event of an emergency** Any death, life-threatening event or other serious adverse event experienced by a subject during the course of the trial, whether or not judged drug-related, must be reported immediately and not later than 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF).	*To align with new sponsor standard safety reporting language*
Title page US Fax: 800-860-7836 Ex-US Fax:+1-224-855-5055 Email:clinicalsafety@horizontherapeutics.com	**Title Page** US Fax: 1-888-814-8653 (toll free, within USA) Ex-US Fax: +44 (0)207-136-1046 Email (worldwide):svc-ags-in-us@amgen.com	*To update with new company structure*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
Sponsor Signature Page	**Removed**	*To change the Sponsor's approver with shift to Amgen processes*
Synopsis – Secondary Objectives and Section 8.2 Secondary Objectives 1.Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on Health Assessment Questionnaire Disability Index [HAQ-DI] after 52 weeks of treatment. 2.Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on Physician Global Assessment (MDGA) after 52 weeks of treatment. 3.Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on Patient Global Assessment (PTGA) after 52 weeks of treatment. 4.Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the Physical Effects subscale of the scleroderma skin patient-reported outcome (SSPRO-18) after 52 weeks of treatment. 5.Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the Physical Limitations subscale of the SSPRO-18 after 52 weeks of treatment. 6.Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the modified Rodnan skin score (mRSS), after 52 weeks of treatment. 7.Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on American College of Rheumatology Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from Baseline in mRSS, HAQ-DI, PTGA, MDGA and FVC % predicted after 52 weeks of treatment.	**Synopsis – Secondary Objectives and Section 8.2 Secondary Objectives** 1.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the modified Rodnan skin score (mRSS), after 52 weeks of treatment. 2.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Revised Composite Response Index in Systemic Sclerosis (Revised CRISS [CRISS 25]) after 52 weeks of treatment. 3.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Health Assessment Questionnaire-Disability Index [HAQ-DI] after 52 weeks of treatment. 4.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Clinician Global Assessment (CGA) after 52 weeks of treatment. 5.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Patient Global Assessment (PTGA) after 52 weeks of treatment. 6.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Physical Effects subscale of the scleroderma skin patient-reported outcome (SSPRO-18) after 52 weeks of treatment. 7.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Physical Limitations subscale of the SSPRO-18 after 52 weeks of treatment.	*To enhance 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 help in global evaluation of likelihood of improvement. The hierarchical testing approach will allow evaluation of the primary and secondary endpoints in the order of statistical and clinical significance.*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
8.Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on ACR-CRISS-20, defined as improvement in ⩾3 core set measures from Baseline of ⩾20% in mRSS, ⩾20% in HAQ-DI, ⩾20% in PTGA, ⩾20% in MDGA and ⩾5% in FVC % predicted after 52 weeks of treatment. 9.Assess safety and tolerability of HZN-825 based on adverse events (AEs), the adverse event of special interest (AESI) [redacted] concomitant medication use, vital signs, 12-lead electrocardiogram (ECG) and clinical safety laboratory evaluations (hematology, chemistry, inflammatory parameters, coagulation panel and urinalysis). 10.Evaluate the pharmacokinetics (PK) of HZN-825.	8.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on proportion of subjects with clinically important change in the mRSS, after 52 weeks of treatment. 9.Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from Baseline in mRSS, HAQ-DI, PTGA, CGA and FVC % predicted after 52 weeks of treatment. 10.Assess safety and tolerability of fipaxalparant (HZN-825) based on adverse events (AEs), the adverse event of special interest (AESI) [redacted], concomitant medication use, vital signs, 12-lead electrocardiogram (ECG) and clinical safety laboratory evaluations (hematology, chemistry, inflammatory parameters, coagulation panel and urinalysis). 11.Evaluate the pharmacokinetics (PK) of fipaxalparant (HZN-825).	
Synopsis – Trial Design The trial will include up to a 42-day Screening Period and a 52-week Double-blind Treatment Period. Subjects will take their first dose of trial drug at the clinic and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. All subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302). Subjects not entering the extension trial will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.	**Synopsis – Trial Design** The trial will include up to a 42-day Screening Period and a 52-week Double-blind Treatment Period. Subjects will take their first dose of trial drug at the clinic and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. All subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302). All Week 52 assessments should be performed before the first dose of the extension trial drug is administered. Subjects not entering the extension trial will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.	*To ensure subjects complete the current study in its entirety before starting the next treatment*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
Synopsis – Trial Design An independent data monitoring committee (IDMC) will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and will include comparative unblinded efficacy and safety data. The IDMC charter will include processes to unblind select Horizon personnel to assess unforeseen issues that may affect dose selection; otherwise, unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management.	**Synopsis – Trial Design** An independent data monitoring committee (IDMC) will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and will include comparative unblinded efficacy and safety data.	*Removed as dose selection is no longer applicable.*
Synopsis – Study Schema, Synopsis - Duration of Treatment and Follow-up, 9.1 Overall Trial Design and Plan, and Figure 9.1 Schematic of Trial Design Subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302).	**Synopsis – Study Schema, Synopsis - Duration of Treatment and Follow-up, 9.1 Overall Trial Design and Plan, and Figure 9.1 Schematic of Trial Design** Subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302). All Week 52 assessments should be performed before the first dose of the extension trial drug is administered.	*To ensure subjects complete the current study in its entirety before starting the next treatment*
Synopsis – Exclusion Criteria and 9.3.2 Exclusion Criteria 21.International normalized ratio >2, prolonged prothrombin time >1.5 × the upper limit of normal (ULN) or partial thromboplastin time >1.5 × ULN at Screening.	**Synopsis – Exclusion Criteria and 9.3.2 Exclusion Criteria** 21.International normalized ratio >2, prolonged prothrombin time >1.5 × the upper limit of normal (ULN) or partial thromboplastin time >1.5 × ULN at Screening (only applicable to the first 110 subjects for whom biopsy will be performed).	*To clarify this is applicable to the first 110 subjects*
Global MDGA	**Global** CGA	*To align with industry-standard language*
Synopsis – Statistical Analysis and Section 9.6.1.2 Secondary Efficacy Endpoints Secondary Efficacy Endpoints	**Synopsis – Statistical Analysis and Section 9.6.1.2 Secondary Efficacy Endpoints** 1.Change from Baseline in the mRSS at Week 52.	*To enhance the ability to demonstrate overall improvement in the disease-Improvement in*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
1.Change from Baseline in HAQ-DI at Week 52. 2.Change from Baseline in MDGA at Week 52. 3.Change from Baseline in PTGA at Week 52. 4.Change from Baseline in the Physical Effects subscale of the SSPRO 18 at Week 52. 5.Change from Baseline 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 Baseline 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 Baseline: ⩾20% in mRSS, ⩾20% in HAQ DI, ⩾20% in PTGA, ⩾20% in MDGA and ⩾5% for FVC % predicted at Week 52 (ACR CRISS 20).	2.Proportion of subjects responding to treatment based on CRISS 25 at Week 52. 3.Change from Baseline in HAQ-DI at Week 52. 4.Change from Baseline in CGA at Week 52. 5.Change from Baseline in PTGA at Week 52. 6.Change from Baseline in the Physical Effects subscale of the SSPRO-18 at Week 52. 7.Change from Baseline 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 Baseline at Week 52. 9.Responder rate (defined as ACR-CRISS [predicted probability] of at least 0.6) at Week 52.	*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. The hierarchical testing approach will allow evaluation of the primary and secondary endpoints in the order of statistical and clinical significance.*
[redacted] 10.Change from Baseline to Week 52 in the mRSS. [redacted]	[redacted]	*To align with updated secondary endpoints.* "*Change from Baseline to Week 52 in the mRSS" is moved from exploratory to the secondary endpoints.*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
[redacted]		
Synopsis – Statistical Analyses – Efficacy and Section 9.6.3 Primary Efficacy Endpoint Analyses Then adjustments for each treatment group (placebo and HZN-825 dose selected for Phase 3) will be added to the imputed data and vary to find conditions with non-significant treatment effect.	**Synopsis – Statistical Analyses – Efficacy and Section 9.6.3 Primary Efficacy Endpoint Analyses** Then adjustments for each treatment group (placebo and fipaxalparant [HZN-825]) will be added to the imputed data and vary to find conditions with non-significant treatment effect.	*Updated to remove specific mention of dose selection.*
Synopsis – Statistical Analyses – Efficacy and Section 9.6.4 Secondary Efficacy Endpoint Analyses The key secondary endpoint for the trial will be change in HAQ-DI from Baseline to Week 52. Analysis will follow that of the primary efficacy endpoint. Statistical significance on change in HAQ-DI will only be concluded if statistical significance was achieved for the primary endpoint.	**Synopsis – Statistical Analyses – Efficacy and Section 9.6.4 Secondary Efficacy Endpoint Analyses** The key secondary endpoint for the trial will be change in mRSS from Baseline to Week 52. Analysis will follow that of the primary efficacy endpoint. Statistical significance on change in mRSS will only be concluded if statistical significance was achieved for the primary endpoint.	*Updated to align with updated key secondary endpoint.*
Synopsis – Statistical Analyses and Section 9.6.10 Multiple Comparisons The overall statistical level is α=0.05 (2-sided). An adjustment will be made to account for the futility analysis at the interim analysis. Even though there is no chance to stop the trial at the futility analysis for conclusion of benefit, a small adjustment to the type I error rate (0.001) will be made to account for the unblinded, comparative summary. Therefore, we will use α=0.049 (2-sided) in the final analysis to evaluate the primary and secondary endpoints as specified.	**Synopsis – Statistical Analyses and Section 9.6.10 Multiple Comparisons** The overall statistical level is α=0.05 (2-sided).	*Unblinded data review is no longer used in this protocol*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
Synopsis – Statistical Analyses and Section 9.6.10 Multiple Comparisons The resulting p-values will be ranked, and the larger p-value will be evaluated at the α = 0.049 (2-sided) threshold. If statistically significant, then both comparisons will be considered significant. If the larger of the two P-values is not statistically significant at α = 0.049 (2-sided), then the smaller P-value will be compared to an α = 0.0245 (2 sided). If 1 or both dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur due to exhaustion of alpha. If both HZN-825 doses are statistically significantly better than the placebo for the primary efficacy endpoint at α = 0.049 (2-sided), the same Hochberg testing procedure will subsequently be used to evaluate the key secondary endpoint. If both dose regimens of HZN-825 for the key secondary endpoint are considered significant, subsequent secondary endpoints will be tested sequentially within each dose in the order presented above, using α = 0.0245 (2-sided) in a sequential testing procedure. If all preceding sequentially tested hypotheses are rejected at α = 0.0245 (2-sided) the next hypothesis will be tested. Once a hypothesis is not rejected, all subsequent endpoints within the same dose will not be tested due to alpha exhaustion. Although p-values will be provided for exploratory endpoints, they will not be used for inferential purposes.	**Synopsis – Statistical Analyses and Section 9.6.10 Multiple Comparisons** The resulting p-values will be ranked, and the larger p-value will be evaluated at the α = 0.05 (2-sided) threshold. If statistically significant, then both comparisons will be considered significant. If the larger of the two P-values is not statistically significant at α = 0.05 (2-sided), then the smaller P-value will be compared to an α = 0.025 (2-sided). If 1 or both dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur due to exhaustion of alpha. If both fipaxalparant (HZN-825) doses are statistically significantly better than the placebo for the primary efficacy endpoint at α = 0.05 (2-sided), the same Hochberg testing procedure will subsequently be used to evaluate the key secondary endpoint. If both dose regimens of fipaxalparant (HZN-825) for the key secondary endpoint are considered significant, subsequent secondary endpoints will be tested sequentially within each dose in the order presented above, using α = 0.025 (2-sided) in a sequential testing procedure. If all preceding sequentially tested hypotheses are rejected at α = 0.025 (2-sided) the next hypothesis will be tested. Once a hypothesis is not rejected, all subsequent endpoints within the same dose will not be tested due to alpha exhaustion.	*To align with removal of unblinded review*
Synopsis – Statistical Analyses -Safety and Tolerability Laboratory values and vital signs will be summarized by treatment received with change from Baseline and with shift tables. Additionally, a shift table for glucose by Common Terminology Criteria for Adverse Events grade and visit will be summarized. Summaries will be provided separately for hyperglycemia.	**Synopsis – Statistical Analyses -Safety and Tolerability** Laboratory values and vital signs will be summarized by treatment received with change from Baseline and with shift tables.	*Removed as no longer applicable*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
Synopsis – Sample Size Estimate Assuming a clinically important difference between HZN-825 and placebo of 4 percentage points and a standard deviation of 8.5, a sample size of 100 subjects per treatment group will provide 85% power to demonstrate an improvement between a dose regimen of HZN-825 and placebo using α=0.024, 2-sided.	**Synopsis – Sample Size Estimate** Assuming a clinically important difference between fipaxalparant (HZN-825) and placebo of 4 percentage points and a standard deviation of 8.5, a sample size of 100 subjects per treatment group will provide 85% power to demonstrate an improvement between a dose regimen of fipaxalparant (HZN-825) and placebo using α=0.025, 2-sided.	*To align with removal of unblinded review*
List of Abbreviations	**List of Abbreviations** CGA Clinician Global Assessment DSUR Development Safety Update Report EU European Union	*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 186 healthy subjects in 8 completed Phase 1 clinical trials and 31 subjects with diffuse cutaneous SSc in a Phase 2a clinical trial. In clinical trials completed as of 03 March 2023, HZN-825 was well-tolerated and showed similar safety and pharmacokinetic profiles across healthy subjects (including elderly healthy subjects) and subjects with diffuse cutaneous SSc.	**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 pharmacokinetic 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 9.5.4.1.1.4).	**Section 7.1.3.4 Clinical Experience** [redacted] therapy that will continue to be monitored as an AE of special interest (AESI) (Section 9.5.4.1.1.4). Additionally, increases in [redacted] have been seen in blinded clinical studies with	*To update in alignment with additional risks observed with use of investigational product*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	fipaxalparant. These events are mostly non-serious and reversible. Liver enzyme elevation will be monitored per FDA guidelines (Section 9.3.3.1).	
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 Based on preliminary PK results from Trial HZNP-HZN-825-101, 300 mg BID dosing with a meal using 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 is selected as the higher dose in this trial.	**Section 7.3 Rationale for Dose Selection** Based on 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 is selected as the higher dose in this trial.	*To remove "preliminary" as results are no longer preliminary*
Section 9.1 Overall Trial Design and Plan A futility analysis will be conducted after approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and these unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC). The IDMC charter will include processes to unblind select Horizon personnel who are not directly involved with the trial conduct to assess unforeseen issues that may involve subject safety or dose selection; otherwise, unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management. The IDMC will also review accumulating safety data to ensure subject safety.	**Section 9.1 Overall Trial Design and Plan** A futility analysis will be conducted after approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and these unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC). The IDMC will also review accumulating safety data to ensure subject safety.	*To align with change in blinding procedures*
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	**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	*To remove option for continued dosage and promote subject safety*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
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.	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.	
Section 9.4.6.1.2 Drug-induced Liver Injury Refer to Section 9.3.3.1 for criteria regarding trial drug discontinuation due to drug-induced liver injury.	**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 transient. 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 9.4.8 Blinding and Unblinding An IDMC will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and will include comparative unblinded efficacy and safety data. The IDMC charter will include processes to unblind select Horizon personnel to assess unforeseen issues that may affect dose selection; otherwise, unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management.	**Section 9.4.8 Blinding and Unblinding** An IDMC will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and will include comparative unblinded efficacy and safety data.	*To align with change in blinding procedures*
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*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
Section 9.5.1.5 Revised Composite Response Index in Systemic Sclerosis (CRISS 25) **New section, subsequent sections re-numbered with this insertion**	**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 FVCpp 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 9.5.1.9.7 Exit Interviews To understand what patients perceive as meaningful in terms of change in some of the patient-reported outcome measures, semi-structured qualitative interviews will be conducted by telephone after the Week 52 Visit (trial exit) at approximately 4 to 5 sites, and with approximately 20 subjects across the US. Participants in the exit interviews will be selected in order to approximate representativeness of the clinical trial population of patients with SSc, with diversity in terms of age, gender, ethnicity, urban/rural practice and geographic area of residence, where possible. The one-on-one, semi-structured, qualitative interviews will provide a greater understanding of the subjects' treatment experience and meaningful change in select patient-reported endpoints, including the global questions of the [redacted] and the SSPRO overall score and domain scores.	**Section 9.5.1.10.7 Exit Interviews** To understand what patients perceive as meaningful in terms of change in some of the patient-reported outcome measures, semi-structured qualitative interviews will be conducted by telephone after the Week 52 Visit (trial exit) in a subset of subjects. The one-on-one, semi-structured, qualitative interviews will provide a greater understanding of the subjects' treatment experience and meaningful change in select patient-reported endpoints and some of the core set measures of the Revised CRISS (CRISS 25).	*To provide flexibility on number of exit interviews, number of sites and countries, and align with CRISS 25*
Section 9.5.4.1.2 Documentation of Adverse Events If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by trial drug, the	**Section 9.5.4.1.2 Documentation of Adverse Events** If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by trial drug, the Investigator will report this SAE using the procedures described	*To align with expected reporting and subject confidentiality*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
Investigator will report this SAE using the procedures described in Section 9.5.4.1.5.	in Section 9.5.4.1.5. 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.	
Section 9.5.4.1.4 Relationship or Causality to Trial Drug The relationship of the trial drug to each AE will be determined by the Investigator and the Sponsor based on the following definitions:	**Section 9.5.4.1.4 Relationship or Causality to Trial Drug** The investigator is obligated to assess the relationship between investigational product(s) and each occurrence of each AE and SAE. Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in their assessment. For each AE/SAE, the investigator must document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which a SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data.	*To align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The relationship of the trial drug to each AE will be determined by the Investigator and the Sponsor based on the following definitions:	
Section 9.5.4.1.5 Reporting and Documenting Serious Adverse Events All SAEs beginning with the time of signing of the ICF and continuing through 4 weeks after the last dose of trial drug must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to trial drug: 1.Report the SAE to the Sponsor by entering the information into the eCRF **immediately, without undue 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 for contact information). 2.Perform appropriate diagnostic tests and therapeutic measures and submit all follow up substantiating data, such as diagnostic test reports, hospital discharge summaries and autopsy report to the Sponsor's representative. 3.Conduct appropriate consultation and follow-up evaluation until the SAE outcome is known or the SAE is resolved. 4.Review each SAE report and evaluate the relationship of the SAE to trial treatment.	**Section 9.5.4.1.5 Reporting and Documenting Serious Adverse Events** All SAEs beginning with the time of signing of the ICF and continuing through 4 weeks after the last dose of trial drug must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to trial drug: 1.Report the SAE to the Sponsor by entering the information into the eCRF **immediately and not later than 24 hours** after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE 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.	*To align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	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	

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	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 9.5.4.1.6 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.	**Section 9.5.4.1.6 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 9.5.4.1.10 Development Safety Update Reports The Sponsor will prepare and submit annual safety reports to the US FDA. Drug safety update reports will also be submitted to countries and territories as required.	**Section 9.5.4.1.10 Development Safety Update Reports** The Sponsor will prepare and submit annual safety reports to the US FDA. Drug safety update reports will also be submitted to countries and territories as required. The Sponsor will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report in the European Union) for the Sponsor Investigational Product. To ensure that consolidated safety information for the study is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical study, if applicable. **9.5.4.1.11 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 (eg, 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 (eg,	*To add the development safety update report to align with recommendations from regulatory agencies and additional sections To align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the external review body, if appropriate according to local requirements. For studies in which the treatment assignment is blinded, to comply with worldwide reporting regulations for SAEs, the treatment assignment of subjects who develop serious, unexpected, and related AEs may be unblinded by the Sponsor before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related SAEs reports sent to regulatory authorities in accordance with local requirements. **9.5.4.1.12 Safety Monitoring Plan** Subject safety will be routinely monitored as defined in the Sponsor's safety surveillance and signal management processes.	
Section 9.5.4.2 Pregnancy Reporting	**Section 9.5.4.2 Pregnancy and Lactation Reporting**	*To better encompass content of this section*
Section 9.5.4.2 Pregnancy Reporting The Investigator should report pregnancies to the Sponsor within 24 hours by submitting the completed pregnancy report form by email to clinicalsafety@horizontherapeutics.com, fax or telephone within 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see Appendix 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 9.5.4.2 Pregnancy and Lactation Reporting** Details of all pregnancies and/or lactation in female subjects and pregnancies in female partners of male subjects will be collected after the start of study treatment and until 4 weeks after last dose of trial drug. If a pregnancy is reported, the investigator is to inform the Sponsor immediately and no later than 24 hours of learning of the pregnancy and/or lactation. The Investigator should report pregnancies to the Sponsor by submitting the completed pregnancy report form immediately and not later than 24 hours after becoming aware that the subject/subject's female partner has become pregnant (see Appendix 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy. If	*To align with new sponsor standard safety reporting language*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	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.	
Section 9.5.6.1 Screening •Enter visit data in the electronic data capture (EDC) system.	**Section 9.5.6.1 Screening** •Enter visit data in the EDC system.	*To align with abbreviation now presented previously.*
Section 9.5.6.2.10 Week 52 (End of Treatment) Subjects who complete the Double-blind Treatment Period (Week 52) will be eligible enter an extension trial, HZNP-HZN-825-302.	**Section 9.5.6.2.10 Week 52 (End of Treatment)** Subjects who complete the Double-blind Treatment Period (Week 52) will be eligible enter an extension trial, HZNP-HZN-825-302. All Week 52 assessments should be performed before the first dose of the extension trial drug is administered.	*To ensure subjects complete the current study in its entirety before starting the next treatment*
Section 9.6.4 Secondary Efficacy Endpoint Analyses The key secondary endpoint for the trial will be change in HAQ-DI from Baseline to Week 52. Analysis will follow that of the primary efficacy endpoint. Statistical significance on change in HAQ-DI will only be concluded if statistical significance was achieved for the primary endpoint. The MDGA, PTGA and Physical Effects and Physical Limitations subscales of the SSPRO-18 will be analyzed analogously to the primary efficacy endpoint.	**Section 9.6.4 Secondary Efficacy Endpoint Analyses** The key secondary endpoint for the trial will be change in mRSS from Baseline to Week 52. Analysis will follow that of the primary efficacy endpoint. Statistical significance on change in mRSS will only be concluded if statistical significance was achieved for the primary endpoint. The proportion of subjects responding to treatment based on CRISS 25 will be evaluated using logistic model. The Revised CRISS (CRISS 25) is defined as improvement in at least 2 components: ⩾5% increase for FVCpp 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	*To align with updated secondary endpoints.*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	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. The CGA, PTGA and Physical Effects and Physical Limitations subscales of the SSPRO-18 will be analyzed analogously to the primary efficacy endpoint.	
Section 9.6.4 Secondary Efficacy Endpoint Analyses Analysis of ACR-CRISS response rate and proportion of subjects with an improvement in $\geqslant$3 of 5 core measures from Baseline will be analogous to that of the mRSS. We will use NRI-MI (Non-Responder Imputation in conjunction with Multiple Imputation) for missing values observed in calculations of mRSS and ACR-CRISS responders at Week 52; and patients who died before Week 52 will be categorized as non-responders.	**Section 9.6.4 Secondary Efficacy Endpoint Analyses** Analyses of ACR-CRISS and Revised CRISS (CRISS 25) response rates will be done using summary statistics and logistic models. We will use NRI-MI (Non-Responder Imputation in conjunction with Multiple Imputation) for missing values observed in calculations of mRSS and ACR-CRISS responders at Week 52; and patients who died before Week 52 will be categorized as non-responders. This same rule will be applied to Revised CRISS (CRISS 25) analysis.	*To provide details for statistical analyses for CRISS 25.*
[redacted]		
Section 9.6.9 Interim Analyses and Synopsis - Efficacy The futility analysis will not be used to make a positive determination of efficacy to stop the trial.	**Section 9.6.9 Interim Analyses and Synopsis - Efficacy** The futility data will be reviewed by the IDMC. But the futility analysis will not be used to make a positive determination of efficacy to stop the trial.	*To clarify that the IDMC will review futility data*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
Figure 9.2 Schematic of Hochberg Testing Procedure Throughout: 0.0245 and 0.049	**Figure 9.2 Schematic of Hochberg Testing Procedure** Throughout: 0.025 and 0.05	*To align with removal of unblinded review*
Section 9.6.11 Sample Size and Power Considerations Assuming a clinically important difference between HZN-825 and placebo of 4 percentage points and a standard deviation of 8.5, a sample size of 100 subjects per treatment group will provide 85% power to demonstrate an improvement between a dose regimen of HZN-825 and placebo using α=0.024, 2-sided.	**Section 9.6.11 Sample Size and Power Considerations** Assuming a clinically important difference between fipaxalparant (HZN-825) and placebo of 4 percentage points and a standard deviation of 8.5, a sample size of 100 subjects per treatment group will provide 85% power to demonstrate an improvement between a dose regimen of fipaxalparant (HZN-825) and placebo using α=0.025, 2-sided.	*To align with removal of unblinded review*
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 (eg 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	*To update requirements for PI responsibilities to report serious breaches per regulatory recommendations*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	•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	
Section 17.1 Administrative Appendix Sponsor Contact forHorizon Therapeutics U.S.A., Inc. Serious Adverse Event ReportingUS Fax: 800-860-7836 Ex US Fax: +1-224-855-5055 Email: clinicalsafety@horizontherapeutics.com	**Section 17.1 Administrative Appendix**	*To align with new sponsor where this information is reported within the associated forms themselves*
Section 17.2 Physician Global Assessment (MDGA)	**Section 17.2 Clinician Global Assessment (CGA)**	*To align with industry-standard language*
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 total bilirubin (TBL) >2 × ULN should be followed by repeat testing (ALT, AST, ALP, 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.	*To align with guidance from regulatory agencies and sponsor.*

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	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	

Text Version 4.0, Amendment 3 22 June 2023	Amended Text Version 5.0, Amendment 4 22 August 2024	Reason for Change
	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 Randomized, Double-blind, Placebo-controlled, Repeat-dose, Multicenter Trial to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of HZN-825 in Patients with Diffuse Cutaneous Systemic Sclerosis	
Protocol Number: HZNP-HZN-825-301	**Phase**: 2b
Protocol Version: 5.0	
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 2 dose regimens of fipaxalparant (HZN-825), a selective antagonist of lysophosphatidic acid receptor-1 ($LPAR_1$), administered once daily (QD) or twice daily (BID) for 52 weeks in the treatment of subjects with diffuse cutaneous systemic sclerosis (diffuse cutaneous SSc).

Primary Objective

The primary objective is to demonstrate the efficacy of 1 or 2 dose regimens of fipaxalparant (HZN-825) versus placebo in subjects with diffuse cutaneous SSc, as determined by a comparison of change in forced vital capacity (FVC) % predicted after 52 weeks of treatment.

Secondary Objectives

1. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the modified Rodnan skin score (mRSS), after 52 weeks of treatment.
2. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Revised Composite Response Index in Systemic Sclerosis (Revised CRISS [CRISS 25]) after 52 weeks of treatment.
3. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Health Assessment Questionnaire-Disability Index [HAQ-DI] after 52 weeks of treatment.
4. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Clinician Global Assessment (CGA) after 52 weeks of treatment.
5. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Patient Global Assessment (PTGA) after 52 weeks of treatment.
6. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Physical Effects subscale of the scleroderma skin patient-reported outcome (SSPRO-18) after 52 weeks of treatment.
7. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Physical Limitations subscale of the SSPRO-18 after 52 weeks of treatment.
8. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on proportion of subjects with clinically important change in the mRSS, after 52 weeks of treatment.
9. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from Baseline in mRSS, HAQ-DI, PTGA, CGA and FVC % predicted after 52 weeks of treatment.
10. Assess safety and tolerability of fipaxalparant (HZN-825) based on adverse events (AEs), the adverse event of special interest (AESI) [redacted], concomitant medication use, vital signs, 12-lead electrocardiogram (ECG) and clinical safety laboratory evaluations (hematology, chemistry, inflammatory parameters, coagulation panel and urinalysis).
11. Evaluate the pharmacokinetics (PK) of fipaxalparant (HZN-825).

[redacted]

Trial Design:

This is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter trial. Subjects will be screened within 6 weeks prior to the Baseline (Day 1) Visit. Approximately 300 subjects who meet the trial eligibility criteria will be randomized on Day 1 in a 1:1:1 ratio to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (HZN-825) 300 mg BID or placebo for 52 weeks. Randomization will be stratified according to Screening use of mycophenolate mofetil (yes/no) and presence of interstitial lung disease (ILD) (yes/no) based on a Screening [redacted] scan.

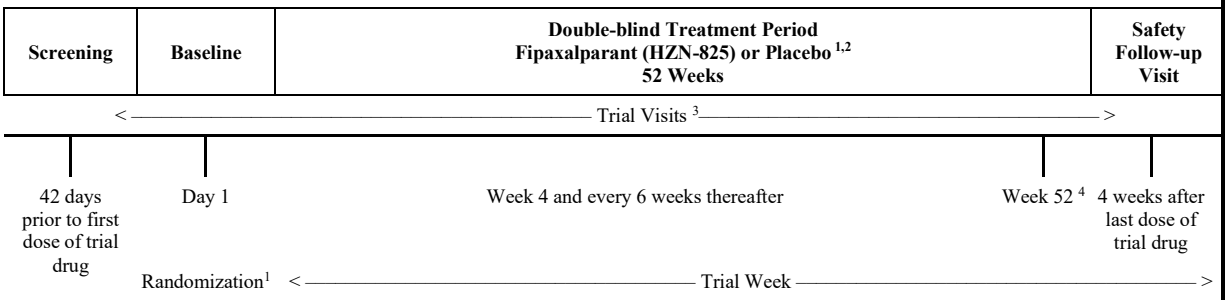
The trial will include up to a 42-day Screening Period and a 52-week Double-blind Treatment Period. Subjects will take their first dose of trial drug at the clinic and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. All subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302). All Week 52 assessments should be performed before the first dose of the extension trial drug is administered. Subjects not entering the extension trial will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.

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

continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 52 assessments. Subjects will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.

An independent data monitoring committee (IDMC) will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and will include comparative unblinded efficacy and safety data.

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



BID=twice daily; QD=once daily

1. Subjects will be randomized in a 1:1:1 ratio to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (HZN-825) 300 mg BID or placebo.
2. If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 52. If a subject prematurely discontinues trial drug and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 52 assessments. Subjects not entering the 52-week extension trial (HZNP-HZN-825-302) will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.
3. Visit windows are ±3 days for Week 4, ±5 days for Week 10 to Week 52, inclusive, and ±14 days for the Safety Follow-up Visit.
4. Subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302). All Week 52 assessments should be performed before the first dose of the extension trial drug is administered.

Subject Population:

Approximately 300 male and non-pregnant female subjects between the ages of 18 and 75 years, inclusive, with diffuse cutaneous SSc will be enrolled.

Inclusion Criteria:

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

1. Written informed consent.
2. Male or female between the ages of 18 and 75 years, inclusive, at Screening.
3. Meets the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc with a total score of ≥9 (Van den Hoogen et al., 2013).
4. Classified as having skin involvement proximal to the elbow and/or knee (diffuse cutaneous SSc subset by LeRoy and Medsger, 2001).
5. At the time of enrollment, less than or equal to 72 months (6 years) since the onset of the first SSc manifestation, other than Raynaud's phenomenon.
6. Skin in the forearm suitable for repeat biopsy (only applicable to the first 110 subjects for whom biopsy will be performed).
7. mRSS units ≥15 at Screening.
8. FVC ≥45% predicted at Screening, as determined by spirometry.
9. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

Exclusion Criteria:

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

1. Positive for anti-centromere antibodies with the exception that subjects who are positive for both anti-centromere and anti-topoisomerase 1 antibodies may be enrolled.
2. Diagnosed with sine scleroderma or limited cutaneous SSc.

3. Diagnosed with other autoimmune connective tissue diseases, except for fibromyalgia, scleroderma-associated myopathy and secondary Sjogren's syndrome.
4. Scleroderma renal crisis diagnosed within 6 months of the Screening Visit (see Section 9.5.1.4).
5. Any of the following cardiovascular diseases:
    a. uncontrolled, severe hypertension (≥160/100 mmHg) or persistent low blood pressure (systolic blood pressure <90 mmHg) within 6 months of Screening,
    b. myocardial infarction within 6 months of Screening,
    c. unstable cardiac angina within 6 months of Screening.
6. DLCO <40% predicted (corrected for hemoglobin). If severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure is of clinical concern for any subject, consider using a DLCO up to 6 months before the Screening Visit.
7. Pulmonary arterial hypertension (PAH) by right heart catheterization requiring treatment with more than 1 oral PAH-approved therapy or any parenteral therapy. Treatment is allowed for erectile dysfunction and/or Raynaud's phenomenon/digital ulcers.
8. Corticosteroid use for conditions other than SSc within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed).
9. Use of any other non-steroid immunosuppressive agent, small biologic molecule, cytotoxic or anti-fibrotic drug within 4 weeks prior to Screening, including cyclophosphamide, azathioprine (Imuran®) or other immunosuppressive or cytotoxic medication. Avoiding the use of listed prohibited treatments must not be considered detrimental and must be indicated by the treating physician. Exceptions include mycophenolate mofetil (CellCept®), mycophenolic acid (Myfortic®), methotrexate and low-dose prednisone, as follows: use of CellCept ≤3 g/day, Myfortic ≤2.14 g/day, methotrexate ≤20 mg/week and prednisone ≤10 mg/day (or equivalent dosing of glucocorticoids) is allowed. See Table 9.1 for full details. Subjects taking CellCept, Myfortic or methotrexate must have been doing so for ≥6 months and the dose must have been stable for ≥4 weeks prior to the Day 1 Visit. Prednisone must have been at a stable dose for ≥8 weeks prior to the Day 1 Visit. It is acceptable to be on background low-dose prednisone and anti-malarial drug along with CellCept, Myfortic or methotrexate. Rituximab must not have been used within 6 months of the Day 1 Visit. Subjects must not be withdrawn from any standard-of-care treatment that is considered necessary for the clinical management of the subject in order to fulfill the trial eligibility requirements.
10. Known active bacterial, viral, fungal, mycobacterial or other infection, including tuberculosis or atypical mycobacterial disease (fungal infections of nail beds are allowed) at the time of randomization.
11. Use of a United States Food and Drug Administration-approved agent for SSc or an investigational agent for any condition within 90 days or 5 half-lives, whichever is longer, prior to Screening or anticipated use during the course of the trial.
12. Malignant condition in the past 5 years (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
13. 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.
14. Pregnant or lactating women.
15. Current drug or alcohol abuse or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the subject.

16. Previous enrollment in this trial or participation in a prior fipaxalparant (HZN-825) or SAR100842 clinical trial.
17. Known history of positive test for human immunodeficiency virus (HIV). HIV testing is optional based on Investigator assessment, institutional practices or local guidelines to rule out suspected HIV or potential for a positive HIV result. Subject consent is required prior to HIV testing.
18. Active hepatitis (any of the following at Screening):

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

    Hepatitis C:
    - positive anti-hepatitis C virus (anti-HCV) and positive HCV RNA.
19. Current alcoholic liver disease, primary biliary cirrhosis or primary sclerosing cholangitis or moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment by Child-Pugh scoring system.
20. Previous organ transplant (including allogeneic and autologous marrow transplant).
21. International normalized ratio >2, prolonged prothrombin time >1.5 × the upper limit of normal (ULN) or partial thromboplastin time >1.5 × ULN at Screening (only applicable to the first 110 subjects for whom biopsy will be performed).
22. Alanine aminotransferase or aspartate aminotransferase >2 × ULN.
23. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 at Screening.
24. Total bilirubin >2 × ULN. Subjects with documented diagnosis of Gilbert's syndrome may be enrolled if their total bilirubin is ≤3.0 mg/dL.
25. Any other condition that, in the opinion of the Investigator, would preclude enrollment in the trial.

Dose Regimen/Route of Administration:

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

Fipaxalparant (HZN-825) 300 mg QD regimen: One set of 2 fipaxalparant (HZN-825) 150 mg tablets in the morning and one set of 2 placebo tablets in the evening.

Fipaxalparant (HZN-825) 300 mg BID regimen: One set of 2 fipaxalparant (HZN-825) 150 mg tablets in the morning and one set of 2 fipaxalparant (HZN-825) 150 mg tablets in the evening.

Placebo regimen: One set of 2 placebo tablets in the morning and these same tablets again in the evening.

Dosage Form, Strength, Formulation and Storage:

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

Duration of Treatment and Follow-up:

The planned duration of the Double-blind Treatment Period is 52 weeks. All subjects who complete the Double-blind Treatment Period will be eligible to enter into a 52-week extension trial (HZNP-HZN-825-302). All Week 52 assessments should be performed before the first dose of the extension trial drug is administered. Subjects not entering the extension trial will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.

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

Efficacy will be assessed by FVC % predicted, CGA, mRSS, ACR-CRISS, patient-reported outcomes (HAQ-DI, [redacted], PTGA, SSPRO-18, [redacted], quality-of-life, [redacted]

Blood samples for fipaxalparant (HZN-825) PK assessment, [redacted]

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

Statistical Analyses:

Primary Efficacy Endpoint

Change in FVC % predicted from Baseline to Week 52.

Secondary Efficacy Endpoints

1. Change from Baseline in the mRSS at Week 52.
2. Proportion of subjects responding to treatment based on CRISS 25 at Week 52.
3. Change from Baseline in HAQ-DI at Week 52.
4. Change from Baseline in CGA at Week 52.
5. Change from Baseline in PTGA at Week 52.
6. Change from Baseline in the Physical Effects subscale of the SSPRO-18 at Week 52.
7. Change from Baseline 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 Baseline at Week 52.
9. Responder rate (defined as ACR-CRISS [predicted probability] of at least 0.6) at Week 52.

[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 intent-to-treat (ITT) analysis set, consisting of all subjects who are randomized to treatment; subjects will be analyzed according to the treatment group to which they were randomized. Safety analyses will be performed on the safety analysis set, consisting of all subjects who receive at least 1 dose or partial dose of trial drug.

Efficacy

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

The primary efficacy endpoint will be change from Baseline in FVC % predicted to Week 52. A mixed model for repeated measures (MMRM) will be fit to the data using observed change in FVC % predicted values from all planned post-Baseline assessments (i.e., Weeks 16, 28, 40 and 52) and including factors used for stratifying randomization as covariates (use of mycophenolate mofetil [yes/no] and presence of ILD [yes/no]). The least squares mean (LS mean) difference in change from 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.

In the tipping point analysis, data from fipaxalparant (HZN-825) and placebo groups will be imputed under an Missing Not at Random (MNAR) assumption. The missing values in each treatment group will be imputed separately based on observed values in each group, respectively. Then adjustments for each treatment group (placebo and fipaxalparant [HZN-825]) will be added to the imputed data and vary to find conditions with non-significant treatment effect.

The key secondary endpoint for the trial will be change in mRSS from Baseline to Week 52. Analysis will follow that of the primary efficacy endpoint. Statistical significance on change in mRSS will only be concluded if statistical significance was achieved for the primary endpoint.

After approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52, a futility analysis on the primary efficacy endpoint will be conducted using unblinded, comparative data. This analysis will have 2 potential outcomes:

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

The futility data will be reviewed by the IDMC. But the futility analysis will not be used to make a positive determination of efficacy to stop the trial.

Conditional power will be used to determine which of the options is chosen, with a conditional power of ≥10% required for at least 1 dose regimen to continue the trial.

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

The overall statistical level is α=0.05 (2-sided).

Since 2 dose regimens of fipaxalparant (HZN-825) will be compared to placebo in the final analysis, adjustment for multiplicity will be used to preserve the family-wise error rate for multiple comparisons in the primary analysis. For the primary endpoint change from Baseline in FVC % predicted at Week 52, a Hochberg testing procedure will be used for the comparisons of fipaxalparant (HZN-825) BID vs. placebo and fipaxalparant

(HZN-825) QD vs placebo. The resulting p-values will be ranked, and the larger p-value will be evaluated at the $\alpha = 0.05$ (2-sided) threshold. If statistically significant, then both comparisons will be considered significant. If the larger of the two P-values is not statistically significant at $\alpha = 0.05$ (2-sided), then the smaller P-value will be compared to an $\alpha = 0.025$ (2-sided). If 1 or both dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur due to exhaustion of alpha. If both fipaxalparant (HZN-825) doses are statistically significantly better than the placebo for the primary efficacy endpoint at $\alpha = 0.05$ (2-sided), the same Hochberg testing procedure will subsequently be used to evaluate the key secondary endpoint. If both dose regimens of fipaxalparant (HZN-825) for the key secondary endpoint are considered significant, subsequent secondary endpoints will be tested sequentially within each dose in the order presented above, using $\alpha = 0.025$ (2-sided) in a sequential testing procedure. If all preceding sequentially tested hypotheses are rejected at $\alpha = 0.025$ (2-sided) the next hypothesis will be tested. Once a hypothesis is not rejected, all subsequent endpoints within the same dose will not be tested due to alpha exhaustion.

Safety and Tolerability

All subjects who receive at least 1 dose or partial dose of trial drug will be included in safety and tolerability analyses. Subjects who receive treatment other than that to which they were randomized will be included in summaries based on treatment received. Subjects who receive more than 1 treatment will be listed separately and included in summaries with the highest dose received. Supplemental analyses based on randomized dose groups for key safety analysis parameters if there are more than 5% patients with dose error in the trial.

AEs will be summarized for all subjects who receive at least 1 dose or partial dose of trial drug, according to treatment received. The number and percentage of subjects who report at least 1 AE, at least 1 AE of Rheumatology Common Toxicity Criteria (RCTC) Grade 3 or higher, at least 1 serious AE and at least 1 AE related to trial drug will be summarized by System Organ Class and Preferred Term, along with the number who discontinue treatment due to an AE. AE rates (events per patient-year of follow-up during dosing) will also be summarized to account for the different treatment durations. [redacted] is prospectively defined as an AESI and will be summarized separately. The exact methods may be used to evaluate AE/SAE risks for individual groups (i.e., QD, BID, and placebo) and difference between 2 groups (QD vs placebo, BID vs placebo).

Laboratory values and vital signs will be summarized by treatment received with change from Baseline and with shift tables.

Concomitant medications will be summarized by treatment received by Anatomical Therapeutic Chemical Level 4 term and Preferred Term.

Sample Size Estimate:

Based on prior trials of tocilizumab [Khanna and Denton et al., 2016; Khanna and Lin et al., 2020] and abatacept [Khanna and Spino et al., 2020] in a similar subject population, change in FVC % predicted is expected to have a standard deviation of 8 to 8.5 percentage points after 52 weeks of treatment. Assuming a clinically important difference between fipaxalparant (HZN-825) and placebo of 4 percentage points and a standard deviation of 8.5, a sample size of 100 subjects per treatment group will provide 85% power to demonstrate an improvement between a dose regimen of fipaxalparant (HZN-825) and placebo using α=0.025, 2-sided.

2.1 Schedule of Assessments

		Double-blind Treatment Period [2]										Safety Follow-up Visit [3]
Trial Visit	**SCR [1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 4 weeks after last dose of trial drug**
Trial Week (W)	**-42 days**	**Day 1 [4]**	**W4**	**W10 [3]**	**W16**	**W22 [3]**	**W28**	**W34 [3]**	**W40**	**W46 [3]**	**W52/PD [5]**	
Visit Window (±days)			**(±3)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±14)**
Informed consent	X											
Review eligibility criteria	X	X										
Demographics	X											
Medical history [6]	X	X										
Weight	X	X					X				X	
Height	X											
Randomization [7]		X										
Trial drug dispensing		X	X	X	X	X	X	X	X	X	X [8]	
Compliance			X	X	X	X	X	X	X	X	X	
mRSS [9]	X	X			X		X		X		X	
FVC % predicted/spirometry	X	X			X		X		X		X	
CGA		X			X		X		X		X	
[redacted]												
Patient-reported outcome assessments												
[redacted]												
PTGA		X			X		X		X		X	
[redacted]												
SSPRO-18		X			X		X		X		X	

		Double-blind Treatment Period [2]										Safety Follow-up Visit [3]
Trial Visit	**SCR [1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 4 weeks after last dose of trial drug**
Trial Week (W)	**-42 days**	**Day 1 [4]**	**W4**	**W10 [3]**	**W16**	**W22 [3]**	**W28**	**W34 [3]**	**W40**	**W46 [3]**	**W52/PD [5]**	
Visit Window (±days)			**(±3)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±14)**
[redacted]												
Anchor questions												
ACR-CRISS (last week)		X			X		X		X		X	
ACR-CRISS (overall health and change since start of trial)							X				X	
FVC (last week)		X			X		X		X		X	
FVC (change since start of trial)							X				X	
HAQ-DI (last week)		X			X		X		X		X	
HAQ-DI (change since start of trial)							X				X	
SSPRO-18 (last week)		X			X		X		X		X	
SSPRO-18 (change since start of trial)							X				X	
Pregnancy test [15]	X	X	X		X		X		X		X	X
Physical examination [16]	X	X					X				X	X
Vital signs [17]	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
12-lead electrocardiogram [18]	X	X	X		X		X				X	
Echocardiogram [18]	X											

		Double-blind Treatment Period [2]										Safety Follow-up Visit [3]
Trial Visit	**SCR [1]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 4 weeks after last dose of trial drug**
Trial Week (W)	**-42 days**	**Day 1 [4]**	**W4**	**W10 [3]**	**W16**	**W22 [3]**	**W28**	**W34 [3]**	**W40**	**W46 [3]**	**W52/PD [5]**	
Visit Window (±days)			**(±3)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±14)**
Clinical laboratory safety tests												
Chemistry [19]	X	X	X	X	X	X	X	X	X	X	X	X
Lipids [20]	X	X					X				X	
Hematology [21]	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation [22]	X			X								
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X
HBV and HCV serology	X											
[redacted]												
PK samples [25]		X	X	X	X		X		X		X	
[redacted]												
Adverse event assessment [28]	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications [29]	X	X	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; [redacted] FVC=forced vital capacity; HAQ-DI=Health Assessment Questionnaire – Disability Index; HBV=hepatitis B virus; HCV=hepatitis C virus; [redacted]; hsCRP=high-sensitivity C-reactive protein; mRSS=modified Rodnan skin score; PD=premature discontinuation; PK=pharmacokinetic; PTGA=Patient Global Assessment; QD=once daily; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SCR=Screening; [redacted]; SSc=systemic sclerosis; [redacted] SSPRO=scleroderma skin patient-reported outcome; VAS=visual analog scale; W=Week; WOCBP=women of childbearing potential

1. Screening procedures can take place over more than 1 day/clinic visit provided consent is obtained first and all assessments are completed within the designated window. An abnormal test during Screening may be repeated once during the Screening Period.

2. Subjects will take fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (HZN-825) 300 mg BID or placebo depending upon randomization.
3. Visits may be conducted as home health visits, as available within local regions.
4. On Day 1 (Baseline), subjects will be randomized and receive the first dose of trial drug in the clinic. All Day 1 assessments should be performed before the first dose of trial drug is administered in the clinic except for the PK sample collected 2-4 hours post dose.
5. If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 52. If a subject prematurely discontinues trial drug and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 52 assessments. Subjects not entering the 52-week extension trial will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.
6. Medical history, including SSc history and treatment, as well as substance use history.
7. Subjects will be randomized in a 1:1:1 ratio to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (HZN-825) 300 mg BID or placebo.
8. For subjects who are entering the extension trial.
9. The assessment should be performed by the Investigator (or designee) who is trained in skin scoring. Except when strictly unavoidable, the same person should perform the assessment at each evaluation during the trial.

[redacted]

15. Perform for WOCBP. Serum pregnancy test at Screening and Week 52 (or as needed). Urine pregnancy tests should also be done every 4 weeks after randomization, which includes both in-clinic testing at scheduled visits prior to dosing (Weeks 1, 4, 16, 28 and 40) and at home (also a ±5-day window) by the subject and reported to the site (Weeks 8, 12, 20, 24, 32, 36, 44 and 48). A urine pregnancy test will also be done at the Safety Follow-up Visit.
16. A complete physical examination, including but not limited to cardiac, pulmonary, neurologic and skin assessments, as well as directed rheumatology assessments [redacted]
17. Vital signs (blood pressure, heart rate, respiratory rate, temperature) will be measured at each trial visit.
18. Additional electrocardiograms or echocardiograms will be conducted, if clinically indicated. An echocardiogram that has been performed within the 3 months prior to Screening can serve as the Baseline echocardiogram if the subject has been clinically stable.
19. Includes total protein, albumin, sodium, glucose, phosphate, potassium, calcium, chloride, bicarbonate, blood urea nitrogen, creatinine, creatine kinase, uric acid, lactate dehydrogenase, hsCRP and liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, total bile acid, total bilirubin and conjugated and unconjugated bilirubin, if applicable). Samples collected at the Day 1 Visit should be collected before the dose of trial drug is administered in the clinic. Subjects should be fasting for Day 1, Week 28 and Week 52/PD.
20. Includes total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides. Samples collected at the Day 1 Visit should be collected before the dose of trial drug is administered in the clinic. Subjects should be fasting for Day 1, Week 28 and Week 52/PD.
21. Includes hemoglobin, hematocrit, red blood cell count (with morphology if blood cell count is abnormal), mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, reticulocyte count, white blood cell count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelet count and erythrocyte sedimentation rate (must be processed within 1 hour of blood draw). Samples collected at the Day 1 Visit should be collected before the dose of trial drug is administered in the clinic.
22. To determine risk of bleeding for [redacted]; includes prothrombin time, partial thromboplastin time, international normalized ratio and fibrinogen. Only the first 110 consenting subjects will have these assessments completed. For subjects taking warfarin or for evaluation of suspected drug-induced liver injury, physicians should monitor the international normalized ratio or other coagulation parameters, as needed.

[redacted]

25. PK samples will be collected at each of the following visits: Day 1 (at 2 to 4 hours after the first dose of trial drug), Week 4 (pre-dose), Week 10 (anytime during the visit), Weeks 16 and 28 (pre-dose and 2 to 4 hours post-dose) and Weeks 40 and 52 (pre-dose). Note: all pre-dose samples will be collected prior to any trial drug administration for the day. For subjects not entering the 52-week extension, a sample will be collected anytime during the Week 52 Visit.

[redacted]

28. Adverse events that occur after signing the informed consent form and prior to dosing on Day 1 will be considered medical history. Adverse events occurring or worsening after the first dose of trial drug through the Safety Follow-up Visit will be considered treatment-emergent adverse events. All adverse events that occur from the signing of informed consent through the Safety Follow-up Visit will be recorded. The subject should be assessed for the development of new onset of scleroderma renal crisis, new onset or worsening of lung fibrosis, new onset of pulmonary arterial hypertension requiring treatment or right heart catheterization or new onset of left ventricular failure.
29. Includes recording of herb/supplement use. See Table 9.1 for restrictions regarding medications.

3 TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

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	area under the concentration-time curve
$AUC_{0\text{-}12h}$	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
COVID-19	coronavirus disease 2019
CRISS 25	Composite Response Index in Systemic Sclerosis 25
C_{trough}	minimum total trough concentration
CYP	cytochrome P450
DOCA	deoxycorticosterone acetate
[redacted]	
DSUR	Development Safety Update Report
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
EU	European Union
[redacted]	
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCV	hepatitis C virus
HIV	human immunodeficiency virus
[redacted]	

Abbreviation	Definition
hsCRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IND	Investigational New Drug
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
LPA	lysophosphatidic acid
$LPAR_1$	lysophosphatidic acid receptor 1
MDGA	Physician Global Assessment
mRSS	modified Rodnan skin score
NRI-MI	non-responder imputation in conjunction with multiple imputation
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
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
[redacted]	
SSc	systemic sclerosis
[redacted]	
SSPRO-18	scleroderma skin patient-reported outcome
TBL	total bilirubin
TEAE	treatment-emergent adverse event
Tsk-1	tight-skin 1
[redacted]	

Abbreviation	Definition
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 figures and tables or in a single paragraph are defined with the relevant figures, tables and paragraphs.

5 ETHICS

5.1 Institutional Review Board/Independent Ethics Committee

The Principal Investigator (Investigator), the Sponsor and/or contract research organization authorized by the Sponsor will submit this protocol, any protocol modifications, the informed consent form (ICF) and all applicable trial documentation to be used in this trial to the appropriate 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 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 cell 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 LPAR1 [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

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

7.1.3.3 Nonclinical Pharmacokinetics

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

In protein binding studies, [^{14}C]- fipaxalparant (HZN-825) was found to be highly protein bound in all species, with fraction bound ranging from 98.94% to 99.97%. Human serum albumin was found to be the major binding protein in human plasma. Additional information regarding the nonclinical pharmacokinetics (PK) studies is provided in the current version of the Investigator's Brochure.

7.1.3.4 Clinical Experience

Fipaxalparant (HZN-825) has been administered to 244 healthy subjects in 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 pharmacokinetic profiles across healthy subjects (including elderly healthy subjects) and subjects with diffuse cutaneous SSc. In the Phase 2a trial, treatment with fipaxalparant (HZN-825) 300 mg twice daily (BID) resulted in numerical improvement form 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 [redacted], overall disease severity and pruritus [Allanore et al., 2018].

No SAEs or severe adverse events (AEs) occurred in Phase 1 trials. Two subjects experienced AEs leading to permanent trial drug discontinuation (*Nausea* and *Abdominal pain in one subject* after receiving fipaxalparant (HZN-825) 300 mg BID and midazolam *and* asymptomatic *COVID-19* in 1 subject after receiving a single dose of fipaxalparant (HZN-825) 300 mg). 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] that will continue to be monitored as an AE of special interest (AESI) (Section 9.5.4.1.1.4). Additionally, increases in [redacted] have been seen in blinded clinical studies with fipaxalparant. 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

Diffuse cutaneous SSc is a rare and devastating autoimmune disease characterized by skin fibrosis, beginning on the fingers and face, that rapidly becomes generalized with internal organ manifestations of fibrosis. The disease carries a high morbidity and mortality rate; patients with diffuse cutaneous SSc have a 10-year survival rate of 55% [Mayes et al., 2003; Varga and Abraham, 2007]. Death is most often caused by lung, heart and kidney involvement [Tyndall et al., 2010; Hao et al., 2017; Pokeerbux et al., 2019].

Currently, there is no effective treatment or cure for generalized SSc. Treatment depends on the symptoms that are present and the organs that are affected and may include medication and surgery [Kowal-Bielecka et al., 2009]. To date, all available therapeutic options (e.g., corticosteroids, methotrexate, cyclophosphamide, azathioprine and mycophenolate mofetil) have demonstrated only limited efficacy and/or have safety issues that impact their use and are not indicated for use in patients with SSc. One treatment, nintedanib, was approved, although it only slows the decline of pulmonary function in adults with interstitial lung disease (ILD) associated with SSc. Additionally, subcutaneous tocilizumab was also approved in the US for slowing the rate of decline in pulmonary function in patients with SSc-associated ILD. The anti-CD20 monoclonal antibody rituximab (Rituxan®) was approved in Japan in 2021 by the Ministry of Health, Labour and Welfare for an additional indication of SSc, but it is not approved for the treatment of SSc in the US and Europe. Thus, there is a substantial unmet clinical need for an effective and well-tolerated treatment for SSc.

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.

7.3 Rationale for Dose Selection

The dose regimens to be evaluated in this trial are 300 mg QD and 300 mg BID with a meal using fipaxalparant (HZN-825) tablets manufactured by [redacted] SRL and Siegfried Barbera S.L.

These regimens are selected based on a comprehensive review of preclinical data assessing in vitro $LPAR_1$ inhibitory activity, information from rodent fibrosis models, Phase 1 PK data and information from a Phase 2a trial in subjects with diffuse cutaneous SSc.

The completed Phase 2a trial in diffuse cutaneous SSc supports the safety and potential efficacy of 300 mg BID for up to 24 weeks of treatment. The exposures and safety profiles of fipaxalparant (HZN-825) in this trial were similar to those previously observed in healthy subjects, and positive changes in mRSS, HAQ-DI and $LPAR_1$ pathway genes were detected. The observed mean steady-state trough concentration (C_{trough}) was 7300 ng/mL in the Phase 2a trial.

Preclinical data also support the fipaxalparant (HZN-825) exposures targeted for this trial. The minimum total C_{trough} in humans needed for inhibition of $LPAR_1$ activity was between 25.3 and 1536 ng/mL based on in vitro potency evaluations. The half-maximal inhibitory concentration (IC_{50}) of fipaxalparant (HZN-825) against $LPAR_1$ activity ranged from 1.1 to 66.8 ng/mL without presence of albumin, corresponding to 25.3 to 1536 ng/mL after adjusting for the 23-fold shift in IC_{50} in the presence of 3.5% albumin (in the range of human plasma albumin level of 3.5 to 4.5 g/dL [Human Albumin 2009]. In a rat deoxycorticosterone acetate (DOCA) salt model, fipaxalparant (HZN-825) reduced cardiac hypertrophy, hydroxyproline levels and kidney damage at 10 mg/kg BID, with a steady-state area under the concentration-time curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) of 12000 ng*h/mL.

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

In summary, the plasma exposures associated with both fipaxalparant (HZN-825) 300 mg QD and 300 mg BID are anticipated to be well-tolerated and have clinical efficacy. The range of exposures achieved with these dose regimens will support efficient dose-range exploration and allow exposure-response evaluation of fipaxalparant (HZN-825) in subjects with SSc to enable selection of an appropriate regimen for replication of results in a second trial and registration.

8 TRIAL OBJECTIVES

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

8.1 Primary Objective

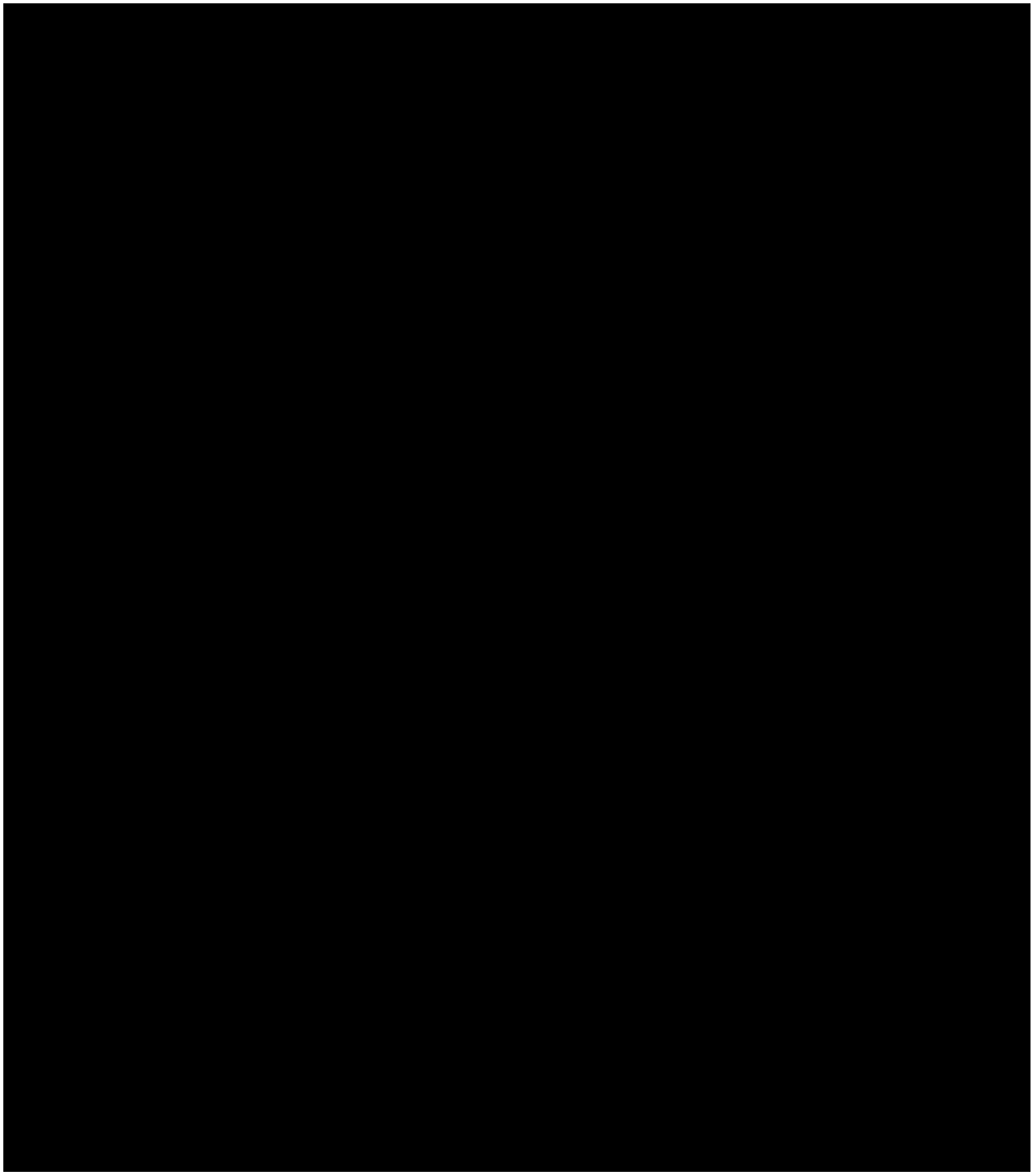
The primary objective is to demonstrate the efficacy of 1 or 2 dose regimens of fipaxalparant (HZN-825) versus placebo in subjects with diffuse cutaneous SSc, as determined by a comparison of change in FVC % predicted after 52 weeks of treatment.

8.2 Secondary Objectives

1. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the modified Rodnan skin score (mRSS), after 52 weeks of treatment.
2. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Revised Composite Response Index in Systemic Sclerosis (Revised CRISS [CRISS 25]) after 52 weeks of treatment.
3. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Health Assessment Questionnaire-Disability Index [HAQ-DI] after 52 weeks of treatment.
4. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Clinician Global Assessment (CGA) after 52 weeks of treatment.
5. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on Patient Global Assessment (PTGA) after 52 weeks of treatment.
6. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Physical Effects subscale of the scleroderma skin patient-reported outcome (SSPRO-18) after 52 weeks of treatment.
7. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on the Physical Limitations subscale of the SSPRO-18 after 52 weeks of treatment.
8. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on proportion of subjects with clinically important change in the mRSS, after 52 weeks of treatment.
9. Evaluate the effect of 2 dose regimens of fipaxalparant (HZN-825) versus placebo on American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from Baseline in mRSS, HAQ-DI, PTGA, CGA and FVC % predicted after 52 weeks of treatment.
10. Assess safety and tolerability of fipaxalparant (HZN-825) based on AEs, the AESI [redacted] concomitant medication use, vital signs, 12-lead

electrocardiogram (ECG) and clinical safety laboratory evaluations (hematology, chemistry, inflammatory parameters, coagulation panel and urinalysis).

11. Evaluate 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 a randomized, double-blind, placebo-controlled, repeat-dose, multicenter trial. Subjects will be screened within 6 weeks prior to the Baseline (Day 1) Visit. Approximately 300 subjects who meet the trial eligibility criteria will be randomized on Day 1 in a 1:1:1 ratio to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (HZN-825) 300 mg BID or placebo for 52 weeks. Randomization will be stratified according to Screening use of mycophenolate mofetil (yes/no) and presence of ILD (yes/no) based on a Screening [redacted] scan.

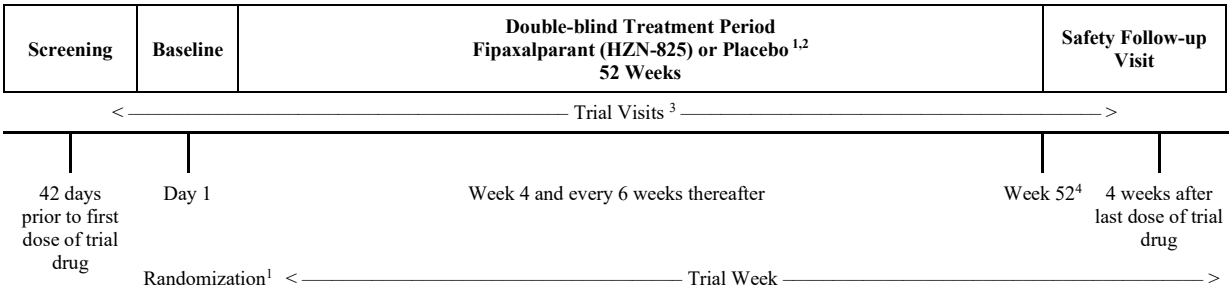
The trial will include up to a 42-day Screening Period and a 52-week Double-blind Treatment Period. Subjects will take their first dose of trial drug at the clinic and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. All subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302). All Week 52 assessments should be performed before the first dose of the extension trial drug is administered. Subjects not entering the extension trial will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.

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

A futility analysis will be conducted after approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and these unblinded efficacy and safety data will be provided to an independent data monitoring committee (IDMC). The IDMC will also review accumulating safety data to ensure subject safety.

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; QD=once daily

1. Subjects will be randomized in a 1:1:1 ratio to receive fipaxalparant (HZN-825) 300 mg QD, fipaxalparant (HZN-825) 300 mg BID or placebo.
2. If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 52. If a subject prematurely discontinues trial drug and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 52 assessments. Subjects not entering the 52-week extension trial (HZNP-HZN-825-302) will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.
3. Visit windows are ±3 days for Week 4, ±5 days for Week 10 to Week 52, inclusive, and ±14 days for the Safety Follow-up Visit.
4. Subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302). All Week 52 assessments should be performed before the first dose of the extension trial drug is administered.

9.1.1 Independent Data Monitoring Committee (IDMC)

An external IDMC will be convened to review data for safety and efficacy, with the possibility of IDMC recommendation on trial design modification per a pre-defined IDMC charter.

The IDMC will include at least 1 statistician and at least 2 clinicians experienced in clinical trials and the therapeutic area. The IDMC charter will include decision rules for stopping the trial based on the comparative, unblinded summary of safety and efficacy. There will be no possibility of stopping the study early for positive efficacy.

9.1.2 Adjudication Committee

A clinical adjudication committee will be established for this trial to adjudicate ACR-CRISS Step 1 events defined in Section 9.5.1.4 that include scleroderma renal crisis, PAH, ILD, left ventricular failure and others. Cause of death will also be adjudicated; a determination will be made if the cause of death is related to SSc or an alternative etiology. The committee will comprise physicians with experience in nephrology, rheumatology and cardiovascular diseases. Periodically, the adjudication committee will review all these events. Details outlining the responsibilities of the adjudication committee and the parameters related to these events of interest will be included in the adjudication committee charter.

9.2 Discussion of Trial Design

This trial is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter trial in 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 would 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], an extension (HZNP-HZN-825-302) of this clinical 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.

A treatment duration of 12 months is appropriate to observe separation from placebo with respect to change in FVC % predicted [Khanna and Denton et al., 2016; Khanna et al., 2018; Distler et al., 2019].

In addition, the ACR-CRISS was developed to show a difference of an active treatment versus placebo at 12 months [Khanna and Berrocal et al., 2016; Khanna et al., 2019].

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. Male or female between the ages of 18 and 75 years, inclusive, at Screening.
3. Meets the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc with a total score of ≥9 [Van den Hoogen et al., 2013].
4. Classified as having skin involvement proximal to elbow and/or knee (diffuse cutaneous SSc subset by LeRoy and Medsger, 2001).
5. At the time of enrollment, less than or equal to 72 months (6 years) since the onset of the first SSc manifestation, other than Raynaud's phenomenon.
6. Skin in the forearm suitable for repeat biopsy (only applicable to the first 110 subjects for whom biopsy will be performed).
7. mRSS units ≥15 at Screening.
8. FVC ≥45% predicted at Screening, as determined by spirometry.
9. 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. Positive for anti-centromere antibodies with the exception that subjects who are positive for both anti-centromere and anti-topoisomerase 1 antibodies may be enrolled.
2. Diagnosed with sine scleroderma or limited cutaneous SSc.
3. Diagnosed with other autoimmune connective tissue diseases except for fibromyalgia, scleroderma-associated myopathy and secondary Sjogren's syndrome.
4. Scleroderma renal crisis diagnosed within 6 months of the Screening Visit (see Section 9.5.1.4).
5. Any of the following cardiovascular diseases:
    a. uncontrolled, severe hypertension (≥160/100 mmHg) or persistent low blood pressure (systolic blood pressure <90 mmHg) within 6 months of Screening,
    b. myocardial infarction within 6 months of Screening,
    c. unstable cardiac angina within 6 months of Screening.
6. DLCO <40% predicted (corrected for hemoglobin). If severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure is of clinical concern for any subject, consider using a DLCO up to 6 months before the Screening Visit.
7. PAH by right heart catheterization requiring treatment with more than 1 oral PAH-approved therapy or any parenteral therapy. Treatment is allowed for erectile dysfunction and/or Raynaud's phenomenon/digital ulcers.
8. Corticosteroid use for conditions other than SSc within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed).
9. Use of any other non-steroid immunosuppressive agent, small biologic molecule, cytotoxic or anti-fibrotic drug within 4 weeks prior to Screening, including cyclophosphamide, azathioprine (Imuran®) or other immunosuppressive or cytotoxic medication. Avoiding the use of listed prohibited treatments must not be considered detrimental and must be indicated by the treating physician. Exceptions include mycophenolate mofetil (CellCept®), mycophenolic acid (Myfortic®), methotrexate and low-dose prednisone, as follows: use of CellCept ≤3 g/day, Myfortic ≤2.14 g/day, methotrexate ≤20 mg/week and prednisone ≤10 mg/day (or equivalent dosing of glucocorticoids) is allowed. See Table 9.1 for full details. Subjects taking CellCept, Myfortic or methotrexate must have been doing so for ≥6 months and the dose must have been stable for ≥4 weeks prior to the Day 1 Visit. Prednisone must have been at a stable dose for ≥8 weeks prior to the Day 1 Visit. It is acceptable to be on background low-dose prednisone and anti-malarial drug along with CellCept, Myfortic or methotrexate. Rituximab must not have been used within 6 months of the Day 1 Visit. Subjects must not be withdrawn from any standard-of-care treatment that is considered necessary for the clinical management of the subject in order to fulfill the trial eligibility requirements.

10. Known active bacterial, viral, fungal, mycobacterial or other infection, including tuberculosis or atypical mycobacterial disease (fungal infections of nail beds are allowed) at the time of randomization .
11. Use of a US Food and Drug Administration-approved agent for SSc or an investigational agent for any condition within 90 days or 5 half-lives, whichever is longer, prior to Screening or anticipated use during the course of the trial.
12. Malignant condition in the past 5 years (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
13. 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.
14. Pregnant or lactating women.
15. Current drug or alcohol abuse or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the subject.
16. Previous enrollment in this trial or participation in a prior fipaxalparant (HZN-825) or SAR100842 clinical trial.
17. Known history of positive test for human immunodeficiency virus (HIV). HIV testing is optional based on Investigator assessment, institutional practices or local guidelines to rule out suspected HIV or potential for a positive HIV result. Subject consent is required prior to HIV testing.
18. Active hepatitis (any of the following at Screening):

Hepatitis B:

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

Hepatitis C:

- positive anti-hepatitis C virus (anti-HCV) and positive HCV RNA.

19. Current alcoholic liver disease, primary biliary cirrhosis or primary sclerosing cholangitis or moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment by Child-Pugh scoring system.
20. Previous organ transplant (including allogeneic and autologous marrow transplant).
21. International normalized ratio (INR) >2, prolonged prothrombin time >1.5 × the upper limit of normal (ULN) or partial thromboplastin time >1.5 × ULN at Screening (only applicable to the first 110 subjects for whom biopsy will be performed).
22. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × ULN.
23. Estimated glomerular filtration rate <30 mL/min/1.73 m^2 at Screening.
24. Total bilirubin >2 × ULN. Subjects with documented diagnosis of Gilbert's syndrome may be enrolled if their total bilirubin is ≤3.0 mg/dL.
25. Any other condition that, in the opinion of the Investigator, would preclude inclusion in 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 trial drug.

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:

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

- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

  Subjects who have ALT or AST levels >3 × ULN confirmed in a repeat test need to undergo close observation as prescribed by the FDA guidance on drug-induced liver injury (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 or use of any rescue medications listed in Table 9.2 prior to Week 28 may lead to subject discontinuation. The investigator may consult with the trial Medical Monitor before initiation of the restricted 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 Double-blind Treatment Period will be encouraged to continue trial participation in all planned visits, particularly returning for the Week 52/premature discontinuation assessments. Subjects who discontinue trial drug due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for

the event is obtained, in addition to being encouraged to continue participation in all planned assessments.

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 (if the subject does not enroll into the extension trial).
- Trial terminated by Sponsor.

9.3.4 Discontinuation of a Treatment Group or the Trial

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

9.3.5 Replacement Policy

9.3.5.1 Subjects

In general, no subject prematurely discontinued from the trial for any reason will be replaced.

9.3.5.2 Centers

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

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

- Excessively slow recruitment.
- Unacceptable protocol adherence.

9.3.5.3 Screen Failures

Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria will be considered screen failures. An abnormal test during Screening may be repeated once during the Screening Period, but results must meet eligibility prior to randomization. Screen failures may be allowed to rescreen for the trial if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that the subject can satisfy all of the eligibility criteria.

9.4 Treatments

9.4.1 Treatments Administered

On Day 1 of the Double-blind Treatment Period, subjects will be randomized in a 1:1:1 ratio to receive:

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

9.4.2 Identity of Investigational Products

9.4.2.1 Fipaxalparant (HZN-825)

Fipaxalparant (HZN-825) is a selective antagonist of $LPAR_1$. Fipaxalparant (HZN-825) will be provided as film-coated tablets for oral administration. The oblong, white tablets contain fipaxalparant (HZN-825) 150 mg and the following excipients: mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, povidone, sodium laurylsulfate, sodium docusate, polyvinyl alcohol, macrogol, titanium dioxide and talc.

9.4.2.2 Placebo

Placebo tablets match the appearance of active tablets and include the following excipients: mannitol, microcrystalline cellulose, magnesium stearate, polyvinyl alcohol, macrogol, titanium dioxide and talc.

9.4.3 Labeling

Fipaxalparant (HZN-825) 150 mg and placebo tablets will be packaged in blinded blister packs according to the dose regimens identified in Section 9.4.1. Trial drug packaging will be in

compliance with Sponsor/contract research organization standard procedures and will meet all local requirements. Each blister pack label will be labeled with a unique number.

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

9.4.4 Storage

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

9.4.5 Drug Accountability

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

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

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

9.4.6 Trial Drug Administration and Timing of Dose for Each Subject

Subjects will take 2 tablets of trial drug (fipaxalparant [HZN-825] 150 mg and/or placebo) orally in the morning and evening with a meal.

Fipaxalparant (HZN-825) 300 mg QD regimen: One set of 2 fipaxalparant (HZN-825) 150 mg tablets in the morning and one set of 2 placebo tablets in the evening.

Fipaxalparant (HZN-825) 300 mg BID regimen: One set of 2 fipaxalparant (HZN-825) 150 mg tablets in the morning and one set of 2 fipaxalparant (HZN-825) 150 mg tablets in the evening.

Placebo regimen: One set of 2 placebo tablets in the morning and these same tablets again in the evening.

In the event a subject misses a dose, the dose should be taken along with the next planned dose (evening or morning) with a meal such that 4 tablets (up to 600 mg) in total will be taken. Due to a less than dose-proportional increase in fipaxalparant (HZN-825) systemic exposure, the 600

mg dose taken in the event of a prior missed dose will be considered part of the planned dosing for this trial.

9.4.6.1 Dose Modifications, Interruptions and Delays

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

9.4.6.1.2 Drug-induced Liver Injury

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

9.4.7 Method of Assigning Subjects to Treatment Groups

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

9.4.8 Blinding and Unblinding

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

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

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

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

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

An IDMC will review unblinded safety and efficacy data on a scheduled basis. A futility analysis will be performed when approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52 and will include comparative unblinded efficacy and safety data.

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 [3]
Steroids for conditions other than diffuse cutaneous SSc	4 weeks prior to Screening through trial completion. Topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed during the trial. Short bursts for acute illnesses (asthma, allergic reaction) are permitted.
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 cyclophosphamide, cyclosporine[1], azathioprine (Imuran®) or other immunosuppressive or cytotoxic medication other than mycophenolate mofetil, mycophenolic acid, low-dose prednisone or an anti-malarial	At least 4 weeks prior to Screening through trial completion. For more details refer to Table 9.2.
Rituximab	6 months prior to the Day 1 Visit through trial completion.
United States Food and Drug Administration-approved agent for SSc or an investigational agent	90 days or 5 half-lives, whichever is longer, prior to Screening through trial completion.
Drug/alcohol abuse	History of abuse within the past 2 years or abuse during trial.
Rifampin[2]	2 weeks prior to dosing through trial completion
OATP inhibitors: clarithromycin, and gemfibrozil. BCRP inhibitor: eltrombopag	3 days prior to dosing through trial completion

BCRP=breast cancer resistance protein; CYP=cytochrome P450; OATP=organic anion transporter polypeptide; PAH=pulmonary arterial hypertension; SSc=systemic sclerosis
1. Cyclosporine is also an OATP and BCRP inhibitor.
2. Rifampicin is a CYP enzyme inducer and an OATP inhibitor.
3. Rescue medications are allowed after Week 28 due to clinically significant deterioration, refer to Table 9.2.

Concomitant treatment with CellCept (mycophenolate mofetil) ≤3 g/day or Myfortic (mycophenolic acid) ≤2.14 g/day, methotrexate ≤20 mg/week and low-dose prednisone (≤10 mg/day) or equivalent dosing of glucocorticoids is allowed during the trial. Subjects taking CellCept, Myfortic or methotrexate must have been doing so for ≥6 months and the dose must have been stable for ≥4 weeks prior to the Day 1 Visit. Subjects taking prednisone must have been at a stable dose for ≥8 weeks prior to the Day 1 Visit.

For subjects taking warfarin, physicians should monitor their INR, as needed. Fipaxalparant (HZN-825) is a weak inhibitor of cytochrome P450 (CYP)2C9, increasing S-warfarin AUC by 23% and R-warfarin AUC by 13% in healthy subjects, with minimal impact on INR (the mean

increase in INR at 24 hours post warfarin administration from Baseline was 14.2% without fipaxalparant (HZN-825) and 16.8% with fipaxalparant (HZN-825) treatment).

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

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

In case of a clinically significant deterioration in SSc, initiation of additional therapy is allowed, as described in Table 9.2, after Week 28. Detailed (S)AE information following such events should be recorded in the eCRF.

Clinically significant deterioration includes:

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

- Relative change since Baseline in mRSS of >25% and an absolute change since 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.

Table 9.2 Rescue Medications Allowed After Week 28 Due to Clinically Significant Deterioration

Medication	Screening Period	Treatment and Post-treatment Follow-up Periods
Non-steroidal medication		
Stable therapy with mycophenolate mofetil/CellCept ≤3 g/day, Myfortic ≤2.14 g/day	Permitted if subject has been receiving for ≥6 months and dose has been stable for ≥4 weeks prior to the Day 1 Visit	Pre-trial dose to be continued except for deterioration [1]
Methotrexate [2] ≤20 mg/week	Permitted if subject has been receiving for ≥6 months and dose has been stable for ≥4 weeks prior to the Day 1 Visit	Pre-trial dose to be continued except for deterioration [1] (≤20 mg/week in any event)
Azathioprine	Not permitted for 4 weeks prior to Screening and throughout Screening	Not permitted except for deterioration [1]
Cyclophosphamide	Not permitted for 4 weeks prior to Screening and throughout Screening	Not permitted except for deterioration [1]
Hydroxychloroquine	Permitted if subject has been receiving for ≥6 months and dose has been stable for ≥4 weeks prior to the Day 1 Visit	Pre-trial dose to be continued except for deterioration [1]
Colchicine, D-penicillamine, sulfasalazine	Not permitted	Not permitted except for deterioration [1]
Rituximab	Not permitted within 6 months prior to the Day 1 Visit	Not permitted except for deterioration [1]
Tocilizumab, abatacept, leflunomide, tacrolimus, newer antiarthritic treatments such as tofacitinib, potassium para-aminobenzoate	Not permitted 6 months prior to Screening	Not permitted except for deterioration [1]
Pirfenidone	Not permitted	Not permitted except for deterioration [1]
Nintedanib	Not permitted	Not permitted except for deterioration [1]
Steroids		
Prednisone >10 mg/day	Not permitted 8 weeks prior to the Day 1 Visit	Not permitted except for deterioration [1]

[redacted]; FVC=forced vital capacity; mRSS=modified Rodnan skin score; OATP=organic anion transporter polypeptide

1. Initiation/change in dose permitted after the Week 28 Visit in case of clinically significant deterioration, defined as:
   - An absolute decline since Baseline in FVC % predicted ≥10% or an absolute decline since Baseline in FVC % predicted ≥5 to 9% with associated decline in [redacted] ≥15% since Baseline, or
   - Relative change since Baseline in mRSS of >25% and an absolute change since 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.
2. Fipaxalparant (HZN-825) is an in vitro inhibitor of organic anion transporters 1 and 3 (OAT1 and OAT3) and may increase the systemic exposures of methotrexate.

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

9.4.10 Treatment Compliance

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

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

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

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

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

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

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 the Investigator (or designee) who is trained in skin scoring. 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 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. Step 1 events will be adjudicated (see Section 9.1.2).

- 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, [redacted] 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.

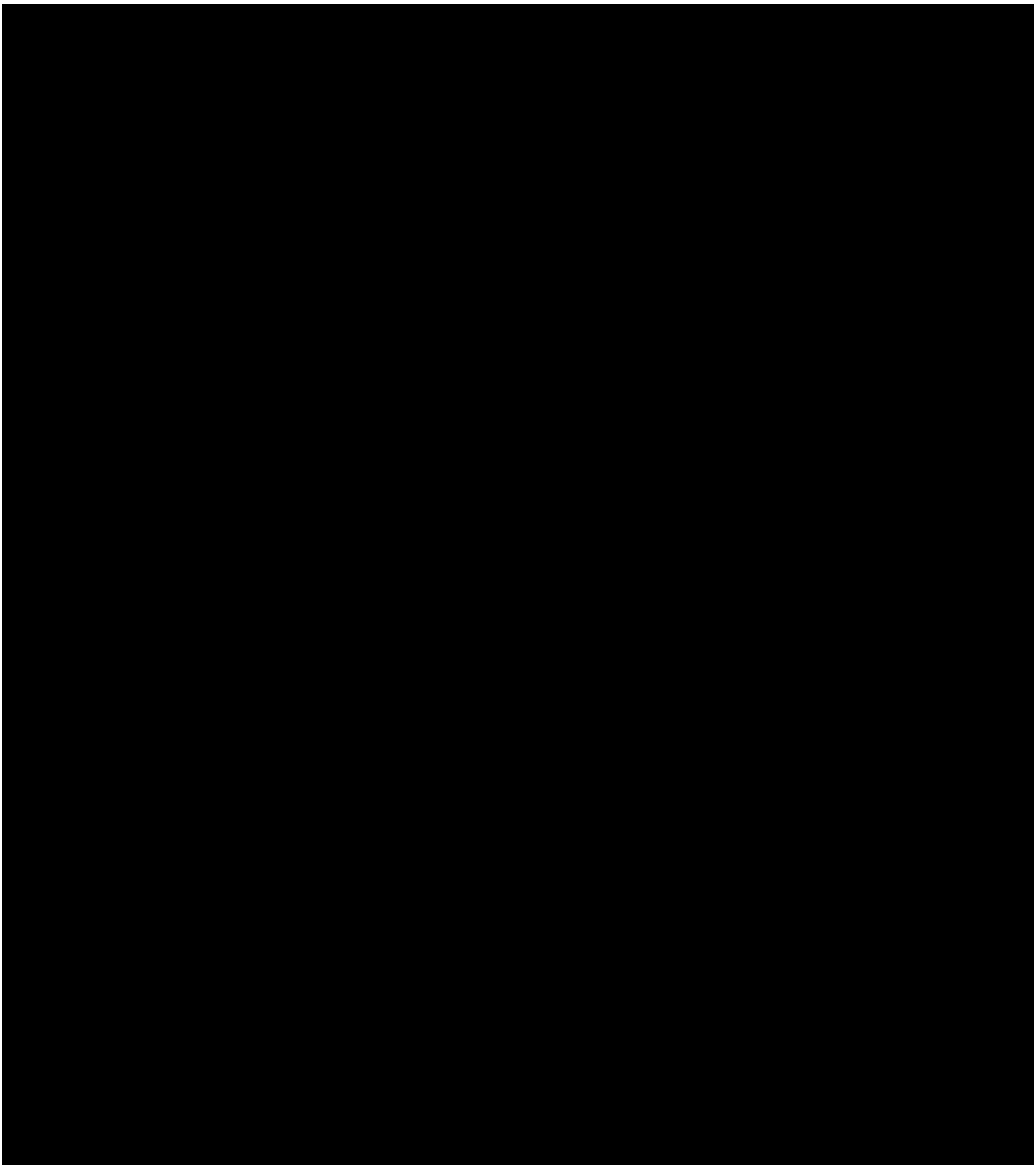
- +3: very much better
- +2: much better
- +1: a little better
- 0: no change
- -1: a little worse
- -2: much worse
- -3: very much worse

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 FVCpp 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.



9.5.1.10 Patient-reported Outcome Assessments

9.5.1.10.1 Health Assessment Questionnaire – Disability Index

The HAQ-DI, which is part of the [redacted] 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.

A copy of the [redacted] is provided in Section [redacted]

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

9.5.1.10.2 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.

A copy of the PTGA is provided in Section 17.5.

9.5.1.10.3 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].

A copy of the SSPRO-18 is provided in Section 17.6.

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.

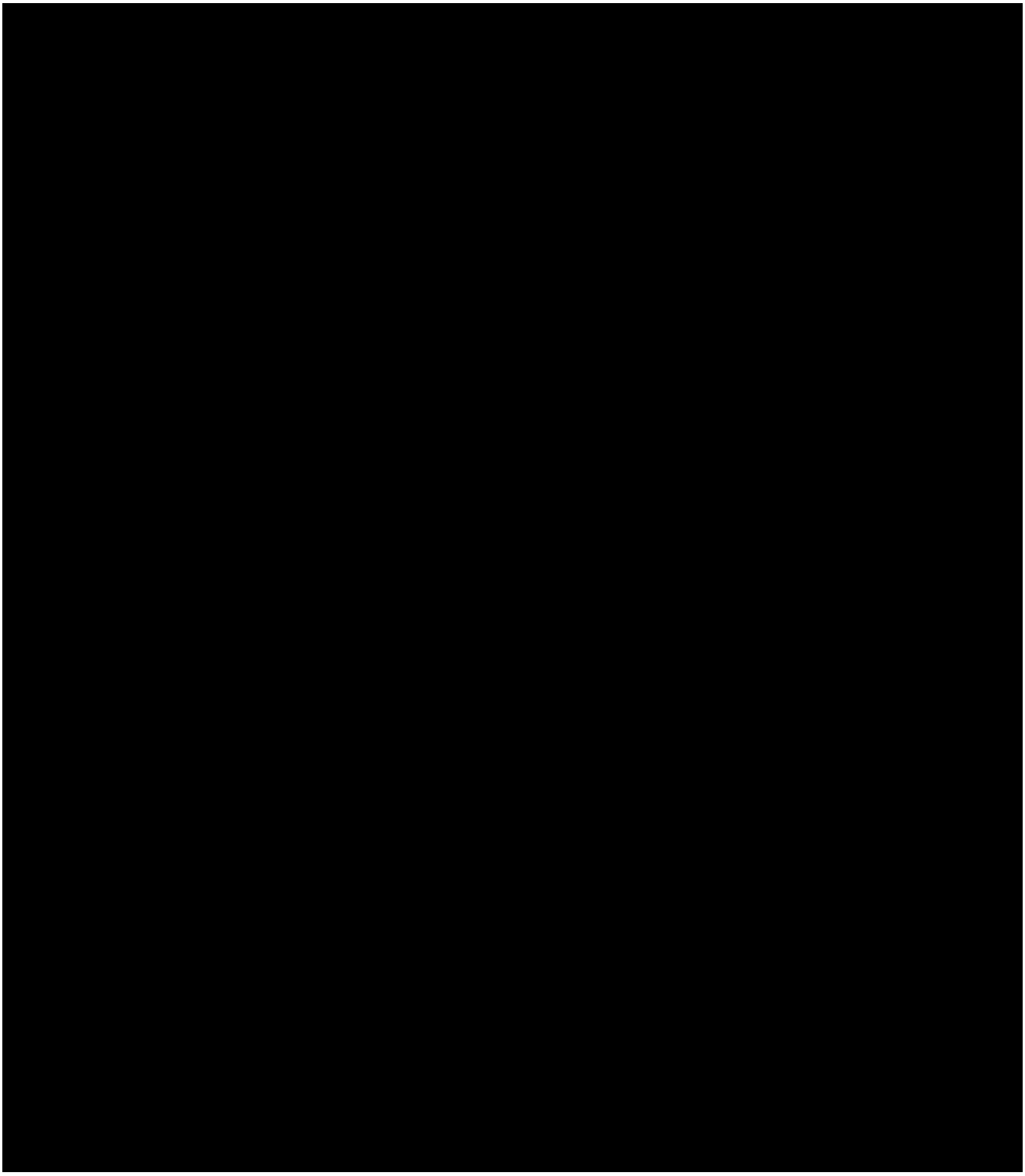
How much did your skin's tightness limit your daily activities in the last week?

- 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

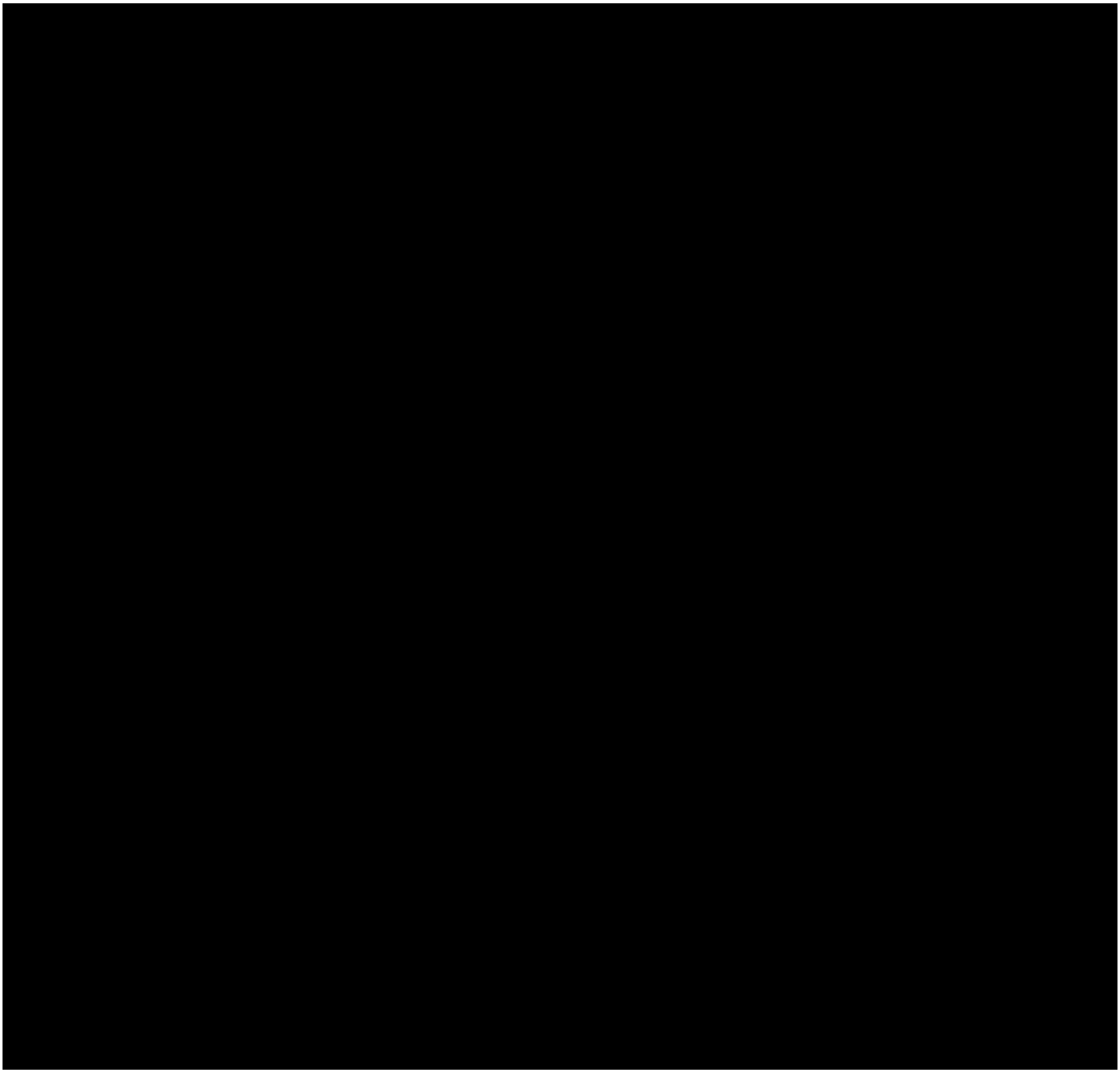


9.5.1.10.7 Exit Interviews

To understand what patients perceive as meaningful in terms of change in some of the patient-reported outcome measures, semi-structured qualitative interviews will be conducted by telephone after the Week 52 Visit (trial exit) in a subset of subjects. The one-on-one, semi-structured, qualitative interviews will provide a greater understanding of the subjects' treatment experience and meaningful change in select patient-reported endpoints and some of the core set measures of the Revised CRISS (CRISS 25).

These interviews are covered and conducted under a separate protocol, and are not part of the schedule of assessments for HZNP-HZN-825-301.

9.5.1.11 Health Status and Systemic Sclerosis-Specific Quality of Life Measures



[redacted]

9.5.2 Pharmacokinetic Measurements

Blood samples will be collected from all subjects to evaluate the PK of fipaxalparant (HZN-825) at the following visits: Day 1 (at 2 to 4 hours after the first dose of trial drug), Week 4 (pre-dose), Week 10 (anytime at the visit), Weeks 16 and 28 (pre-dose and 2 to 4 hours post-dose) and Weeks 40 and 52 (pre-dose). For the Day 1, Week 16 and Week 28 Visits with post-dose PK samples, the first (Day 1) or morning (Weeks 16 and 28) dose regimen will be taken in the clinic. Note that all pre-dose samples will be collected prior to any trial drug administration during the clinic visit. For subjects not entering the 52-week extension trial, a sample will be collected anytime during the Week 52 Visit. PK sample collection time and the most recent dosing time prior to PK sample collection will be recorded for all PK samples.

If the clinic visit is in the morning, on days when a pre-dose PK sample will be collected (i.e., Weeks 4, 16, 28, 40 and 52), subjects will be instructed to withhold taking trial drug before the visit and drug will be administered in the clinic with a meal after the pre-dose PK samples are taken. Time of drug administration in the clinic as well as the most recent dosing time prior to the visit will be recorded; 1 additional PK sample will be collected 2 to 4 hours after dosing in the clinic for during the Week16 and Week 28 Visits.

If the clinic visit is in the afternoon, on days when a pre-dose PK sample will be collected (i.e., Weeks 4, 16, 28, 40 and 52), subjects will be instructed to take trial drug before 8 a.m. with a meal and record dosing time; 1 PK sample will be collected anytime during the clinic. For the Week 16 and Week 28 Visits, subjects will receive the evening dose during the visit (dosing time to be recorded) if it is at least 8 hours from the morning dosing. An additional PK sample will be collected 2 to 4 hours post-dose; otherwise, subjects will be instructed to take the evening dose at regular dosing time and no post-dose PK sample will be collected.

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

[redacted]

[redacted]

9.5.4 Safety Variables

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

9.5.4.1 Adverse Events

9.5.4.1.1 Definitions

9.5.4.1.1.1 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.

9.5.4.1.1.2 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.

9.5.4.1.1.3 Non-serious Adverse Event Definition

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

9.5.4.1.1.4 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] procedure will be performed as outlined in Section 2.1 on Day 1 and at Weeks 4, 28 and 52/premature discontinuation, as detailed in the [redacted] in Section [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 above symptoms are reported by the subject throughout the assessment, without the blood pressure reductions noted above, then the symptoms will only be recorded separately as AEs if they meet any of the criteria below, and [redacted] will not be recorded.

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

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.

9.5.4.1.2 Documentation of Adverse Events

Any AEs that occur after signing the ICF and prior to dosing on Day 1 will be considered medical history. The TEAE reporting period begins with administration of the first dose of trial drug on Day 1 and continues until 4 weeks after the last dose of trial drug or premature discontinuation. All medical history, TEAEs and AEs must be recorded in the source documents and on the subject's eCRF. All AEs and SAEs with onset after signing of informed consent through 4 weeks after the last dose of trial drug will be recorded. If a subject discontinues due to an SAE, that subject will be followed per Section 9.5.4.1.5.

If the Investigator observes an SAE after trial completion that he/she believes was possibly caused by trial drug, the Investigator will report this SAE using the procedures described in Section 9.5.4.1.5. 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.

9.5.4.1.3 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), trial drug continued
- Grade 3 (severe) – prolonged symptoms, reversible, major functional impairment, prescription medications/partial relief, hospitalized <24 hours, temporary trial drug discontinuation or/and dose reduced
- Grade 4 (includes life-threatening) – at risk of death, substantial disability, especially if permanent, hospitalized >24 hours, permanent trial drug discontinuation

9.5.4.1.4 Relationship or Causality to Trial Drug

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

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

The investigator will use clinical judgment to determine the relationship.

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

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

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

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

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

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

- Not related: There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event.
- Related: There is evidence in favor of a causal relationship (i.e., there is a plausible time course) and at least one of the following criteria apply:
    - There is a reasonable pharmacological relationship (or known class effect).
    - There is no other more plausible explanation.
    - There is a positive de-challenge (without active treatment of the event).
    - There is a positive re-challenge.
    - There is a distinguishable dose effect.

9.5.4.1.5 Reporting and Documenting Serious Adverse Events

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

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

9.5.4.1.5.1 Monitoring of Serious Adverse Events Anticipated in the Trial Population

SAEs are anticipated to occur in the trial population independent of the subject's exposure to trial drug. These anticipated SAEs are provided in Section 17.13 (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.

9.5.4.1.6 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.

9.5.4.1.7 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 9.5.4.1.2 and 9.5.4.1.5, 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.

9.5.4.1.8 Review of Adverse Events and Emerging New Safety Information

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

9.5.4.1.9 Reporting of Investigational New Drug Safety Reports

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

9.5.4.1.10 Development Safety Update Reports

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

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

9.5.4.1.11 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 (eg, 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 (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the external review body, if appropriate according to local requirements.

For studies in which the treatment assignment is blinded, to comply with worldwide reporting regulations for SAEs, the treatment assignment of subjects who develop serious, unexpected, and related AEs may be unblinded by the Sponsor before submission to regulatory authorities.

Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related SAEs reports sent to regulatory authorities in accordance with local requirements.

9.5.4.1.12 Safety Monitoring Plan

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

9.5.4.2 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. Serum pregnancy test will be analyzed at Screening and Week 52 (or as needed). Urine pregnancy tests should also be done every 4 weeks after randomization, which includes both in-clinic testing at scheduled visits prior to dosing (Weeks 1, 4, 16, 28 and 40) and at home (also a ±5-day window) by the subject and reported to the site (Weeks 8, 12, 20, 24, 32, 36, 44 and 48). 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 Double-blind Treatment Period, she should immediately notify the Investigator and trial drug dosing should be permanently discontinued but the subject will be asked to continue in the trial for evaluations.

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

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

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
    - Oral
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)

- Bilateral tubal ligation
- 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 Appendix 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.

9.5.4.3 Medical History

Medical history, including diffuse cutaneous SSc history and treatment and substance use history, will be recorded.

9.5.4.4 Vital Signs, Weight and Height

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

[redacted]

9.5.4.6 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 per the Schedule of Assessments (Section 2.1).

9.5.4.7 Electrocardiogram

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

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

9.5.4.8 Echocardiogram

A standard transthoracic echocardiogram will be conducted at Screening. However, an echocardiogram that has been performed within the 3 months prior to Screening can serve as the 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.

9.5.4.9 Laboratory Tests for Evaluation

A central trial laboratory will be used for all protocol-specified laboratory evaluations, with the exception of urine pregnancy tests that will be performed locally at each site 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 (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, total bile acid, total bilirubin, conjugated and unconjugated bilirubin, if applicable).

Lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, 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.

Samples for clinical inflammatory laboratory evaluations (hsCRP and ESR) will also be collected.

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.

To determine risk of bleeding for [redacted], a coagulation profile, including prothrombin time, partial thromboplastin time, INR and fibrinogen, will be performed at Screening prior to any biopsy and at Week 10. Only the first 110 consenting subjects will have these assessments completed. For subjects taking warfarin or for evaluation of suspected drug induced liver injury, physicians should monitor the international normalized ratio or other coagulation parameters, as needed.

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

9.5.5 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], [redacted] SSPRO-18 [Man et al., 2017], [redacted] have been validated for use in subjects with SSc.

9.5.6 Trial Procedures

Subjects who provide informed consent and who meet all the entry criteria for participation in this trial will be randomized.

Select visits may be completed at an alternative remote location, e.g., a subject's home, by a visiting home healthcare professional. 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.

9.5.6.1 Screening

Due to the large number of Screening assessments, the Screening Visit may be completed in more than 1 day. During the Screening Visit, potential trial subjects will be informed fully regarding the nature of the trial and possible AEs and will receive a copy of the ICF for review. Potential trial subjects must read the ICF and sign the document after the Investigator has answered all questions to the trial candidate's satisfaction. Further procedures can begin only after the ICF has been signed. The original signed ICF will be retained by the Investigator and a copy will be given to the trial subject.

Trial candidates will be evaluated for trial entry according to the stated inclusion and exclusion criteria (Section 9.3). The Investigator will evaluate the results of all examinations, including clinical laboratory tests and will determine each candidate's suitability for the trial. The Investigator must review the results of all Screening tests before determining that a candidate is eligible for trial drug treatment. The serum pregnancy test performed at Screening on all WOCBP must be negative for those subjects to be eligible for initiation of treatment. All Screening procedures must be completed within 42 days prior to Day 1 (i.e., the first day of administration of trial drug). The following procedures will be performed during Screening to establish each candidate's general health and eligibility for enrollment into the trial:

- Obtain signed, written informed consent and permission to use Protected Health Information (in accordance with the Health Insurance Portability and Accountability Act). Refusal to provide this permission excludes an individual from eligibility for trial participation. Record date and time informed consent was given and who conducted the process on the appropriate source documentation.
- Determine trial eligibility through review of the inclusion/exclusion criteria (see Section 9.3).
- Obtain demographics.
- Obtain medical history, including diffuse cutaneous SSc history and treatment, as well as substance use history.
- Inquire about prior medications (see Table 9.1 for restrictions regarding medications).
- Query subjects regarding signs and symptoms.
- Measure weight and height.

- Perform physical examination, including the directed rheumatology assessments [redacted].
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Perform 12-lead ECG.
- Perform echocardiogram.
- Perform [redacted] If SARS-CoV-2 exposure is of clinical concern for any subject, consider using a [redacted] up to 6 months before the Screening Visit and measure hemoglobin at Screening to make a correction.
- Collect a blood sample for autoantibodies.
- Collect blood samples for hematology, coagulation, chemistry (including ESR and hsCRP) and hepatitis serology for all subjects, and pregnancy testing for WOCBP (only the first 110 consenting subjects will have their coagulation profile assessed).
- Collect a blood sample for lipid profile.
- Collect urine sample for urinalysis.
- Record mRSS.
- Measure FVC % predicted and ask the FVC % predicted anchor question.
- If no [redacted] is available within the last 3 months, perform Baseline lung [redacted] only after meeting all other eligibility and in time to receive reading prior to randomization.
- Enter visit data in the EDC system.

9.5.6.2 Double-blind Treatment Period

Once randomized into the Double-blind Treatment Period, 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/premature discontinuation assessments. Subjects not entering the 52-week extension trial (HZNP-HZN-825-302) will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug.

9.5.6.2.1 Day 1/Baseline

On Day 1, subjects will return to the clinic for Baseline assessments, randomization and the first dose of trial drug. Subjects should be fasting for this visit.

- Perform review of inclusion/exclusion criteria.
- Review medical history.
- Query subjects regarding signs and symptoms and medications since Screening.
- Measure weight.
- Perform physical examination, including the directed rheumatology assessments [redacted].
- Measure pre-dose vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Perform pre-dose CCI [redacted].
- Perform pre-dose 12-lead ECG.
- Collect pre-dose blood samples for hematology and chemistry (including ESR and hsCRP) analysis.
- Collect a pre-dose blood sample for lipid profile.
- Collect pre-dose urine sample for urinalysis and also for pregnancy testing for WOCBP; the pregnancy test must be negative for the subject to receive trial drug.
- [redacted]
- [redacted]
- [redacted]
- Measure Baseline (pre-dose) FVC % predicted.
- Complete the Baseline (pre-dose) mRSS, [redacted] PTGA and CGA assessments.
- Complete the [redacted] and SSPRO-18 pre-dose.

- Ask the FVC % predicted, HAQ-DI, ACR-CRISS (overall health in last week) and SSPRO-18 anchor questions.
- Complete the [redacted] and [redacted] pre-dose.
- Dispense handheld electronic diary device, provide subject instruction and ask the subject to complete the [redacted] using the device.
- Obtain randomization assignment and trial drug dosing information from the IRT system.
- Dispense trial drug.
- Administer dose of trial drug and record dosing time.
- Collect a blood sample for PK analysis 2 to 4 hours post-dose; record date/time of sample.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Day 1 procedures have been completed and instructed to return for a clinic visit at Week 4.

9.5.6.2.2 Week 4

- Query subjects regarding AEs and concomitant medications.
- Assess trial drug compliance.
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Perform [redacted]
- Perform 12-lead ECG.
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis.
- Collect urine sample for urinalysis and also for pregnancy testing for WOCBP; the pregnancy test must be negative for the subject to receive trial drug.
- Collect a pre-dose blood sample for PK analysis; record date/time of sample. Record date and time of last dose prior to visit.
- [redacted]

- Dispense urine pregnancy test kit for at-home use at Week 8 for WOCBP; contact the subject at Week 8 to obtain pregnancy test results.
- Dispense trial drug.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Week 4 procedures have been completed and instructed to attend a trial visit at Week 10.

9.5.6.2.3 Week 10

- Query subjects regarding AEs and concomitant medications.
- Assess trial drug compliance.
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Collect blood samples for hematology, coagulation and chemistry (including ESR and hsCRP) analysis (only the first 110 consenting subjects will have their coagulation profile assessed).
- Collect urine sample for urinalysis.
- Collect a blood sample for PK analysis anytime during the visit; record date/time of sample. Record date and time of last dose prior to visit.
- Dispense urine pregnancy test kit for at-home use at Week 12 for WOCBP; contact the subject at Week 12 to obtain pregnancy test results.
- Dispense trial drug.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Week 10 procedures have been completed and instructed to return for a clinic visit at Week 16.

9.5.6.2.4 Week 16

- Query subjects regarding AEs and concomitant medications.
- Assess trial drug compliance.
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.

- Perform 12-lead ECG.
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis.
- Collect urine sample for urinalysis and also for pregnancy testing for WOCBP; the pregnancy test must be negative for the subject to receive trial drug.
- [redacted]
- Measure FVC % predicted.
- Complete the mRSS, [redacted] PTGA and CGA assessments.
- Complete the [redacted] and SSPRO-18.
- Ask the FVC % predicted, ACR-CRISS (overall health in last week), HAQ-DI and SSPRO-18 anchor questions.
- Complete the [redacted] and [redacted].
- Collect a pre-dose blood sample for PK analysis; record date/time of sample. Record date and time of last dose prior to visit.
- Administer dose of trial drug and record dosing time.
- Dispense urine pregnancy test kit for at-home use at Week 20 for WOCBP; contact the subject at Week 20 to obtain pregnancy test results.
- Dispense trial drug.
- Collect a blood sample for PK analysis 2 to 4 hours post-dose; record date/time of sample.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Week 16 procedures have been completed and instructed to attend a trial visit at Week 22.

9.5.6.2.5 Week 22

- Query subjects regarding AEs and concomitant medications.
- Assess trial drug compliance.

- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis.
- Collect urine sample for urinalysis.
- Dispense urine pregnancy test kit for at-home use at Week 24 for WOCBP; contact the subject at Week 24 to obtain pregnancy test results.
- Dispense trial drug.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Week 22 procedures have been completed and will be instructed to return to the clinic at Week 28.

9.5.6.2.6 Week 28

Subjects should be fasting for this visit.

- Query subjects regarding AEs and concomitant medications.
- Measure weight.
- Assess trial drug compliance.
- Perform physical examination, including the directed rheumatology assessments [redacted].
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Perform [redacted]
- Perform 12-lead ECG.
- Perform [redacted] (within ±2 weeks of visit date).
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis.
- Collect a blood sample for lipid profile.

- Collect urine sample for urinalysis and also for pregnancy testing for WOCBP; the pregnancy test must be negative for the subject to receive trial drug.
- Measure FVC % predicted.
- Complete the mRSS, [redacted] PTGA and CGA assessments.
- Complete the [redacted] and SSPRO-18.
- Ask the FVC % predicted, HAQ-DI, ACR-CRISS (overall health in last week, and since start of trial) and SSPRO-18 anchor questions.
- Complete the [redacted] and [redacted].
- Collect a pre-dose blood sample for PK analysis; record date/time of sample. Record date and time of last dose prior to visit.
- [redacted]
- Administer trial drug and record the dosing time.
- Dispense urine pregnancy test kit for at-home use at Week 32 for WOCBP; contact the subject at Week 32 to obtain pregnancy test results.
- Dispense trial drug.
- Collect a blood sample for PK analysis 2 to 4 hours post-dose; record date/time of sample.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Week 28 procedures have been completed and will be instructed to attend a trial visit at Week 34.

9.5.6.2.7 Week 34

- Query subjects regarding AEs and concomitant medications.
- Assess trial drug compliance.
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis.

- Collect urine sample for urinalysis.
- Dispense urine pregnancy test kit for at-home use at Week 36 for WOCBP; contact the subject at Week 36 to obtain pregnancy test results.
- Dispense trial drug.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Week 34 procedures have been completed and instructed to return for a clinic visit at Week 40.

9.5.6.2.8 Week 40

- Query subjects regarding AEs and concomitant medications.
- Assess trial drug compliance.
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis.
- Collect urine sample for urinalysis and also for pregnancy testing for WOCBP; the pregnancy test must be negative for the subject to receive trial drug.
- Measure FVC % predicted.
- Complete the mRSS, [redacted] PTGA and CGA assessments.
- Complete the [redacted] and SSPRO-18.
- Ask FVC % predicted, HAQ-DI, ACR-CRISS (overall health in last week) and SSPRO-18 anchor questions.
- Complete the [redacted] and [redacted].
- Collect a pre-dose blood sample for PK analysis; record date/time of sample. Record date and time of last dose prior to visit.
- Dispense urine pregnancy test kit for at-home use at Week 44 for WOCBP; contact the subject at Week 44 to obtain pregnancy test results.
- Dispense trial drug.

- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Week 40 procedures have been completed and instructed to attend a trial visit at Week 46.

9.5.6.2.9 Week 46

- Query subjects regarding AEs and concomitant medications.
- Assess trial drug compliance.
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis.
- Collect urine sample for urinalysis.
- Dispense urine pregnancy test kit for at-home use at Week 48 for WOCBP; contact the subject at Week 48 to obtain pregnancy test results.
- Dispense trial drug.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial center after all of the Week 46 procedures have been completed and instructed to return for a clinic visit at Week 52.

9.5.6.2.10 Week 52 (End of Treatment)

Week 52 is the final visit of the Double-blind Treatment Period. Subjects should be fasting for this visit.

- Query subjects regarding AEs and concomitant medications.
- Assess trial drug compliance.
- Measure weight.
- Perform physical examination, including the directed rheumatology assessments [redacted].
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.

- Perform [redacted]
- Perform 12-lead ECG.
- Perform [redacted] (within ±2 weeks of visit date).
- Collect a blood sample for autoantibodies.
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis for all subjects and pregnancy testing for WOCBP; the pregnancy test must be negative for the subject to receive trial drug in the extension trial.
- Collect a blood sample for lipid profile.
- Collect urine sample for urinalysis.
- Measure FVC % predicted.
- Complete the mRSS, [redacted] PTGA and CGA assessments.
- Complete the [redacted] and SSPRO-18.
- Ask FVC % predicted, HAQ-DI, ACR-CRISS (overall health in last week and since start of trial) and SSPRO-18 anchor questions.
- Complete the [redacted] and [redacted].
- Perform lung [redacted]
- Perform patient interview to conduct cognitive debriefing and concept elicitation, if applicable.
- Collect blood sample for PK analysis; record date/time of sample. Record date and time of last dose prior to visit. For subjects entering the extension trial, this sample is collected before the subject takes any trial drug under that protocol.
- [redacted].
- Dispense trial drug to subjects who elect to enroll in the extension trial.
- Enter visit data in the EDC system.

Subjects who complete the Double-blind Treatment Period (Week 52) will be eligible enter an extension trial, HZNP-HZN-825-302. All Week 52 assessments should be performed before the first dose of the extension trial drug is administered.

9.5.6.3 Safety Follow-up Visit

Subjects not entering the extension trial will participate in a Safety Follow-up Visit 4 weeks after the last dose of trial drug. This visit is not applicable to subjects who have completed all other trial visits and enter the extension trial.

- Query subjects regarding AEs and concomitant medications.
- Perform physical examination, including the directed rheumatology assessments [redacted].
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature) according to standardized instructions.
- Collect blood samples for hematology and chemistry (including ESR and hsCRP) analysis.
- Collect urine sample for urinalysis and also for pregnancy testing for WOCBP.
- Enter visit data in the EDC system.

Subjects will be discharged from the trial after all of the Safety Follow-up Visit procedures have been completed.

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

9.5.6.4 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. A telephone visit, virtual visit or home visit may be used to collect information on AEs and drug compliance. Investigators may also consider shipping trial drug to a subject's home via appropriate courier, if necessary.
- If data are captured in an irregular manner (e.g., patient-reported outcomes via phone 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

9.6.1.1 Primary Efficacy Endpoint

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

9.6.1.2 Secondary Efficacy Endpoints

1. Change from Baseline in the mRSS at Week 52.
2. Proportion of subjects responding to treatment based on CRISS 25 at Week 52.
3. Change from Baseline in HAQ-DI at Week 52.
4. Change from Baseline in CGA at Week 52.
5. Change from Baseline in PTGA at Week 52.
6. Change from Baseline in the Physical Effects subscale of the SSPRO-18 at Week 52.
7. Change from Baseline 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 Baseline at Week 52.
9. Responder rate (defined as ACR-CRISS [predicted probability] of at least 0.6) at Week 52.

[redacted]

9.6.1.4 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.

9.6.1.5 Pharmacokinetic Endpoint

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

9.6.2 Analysis Sets

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

9.6.3 Primary Efficacy Endpoint Analysis

The estimand for the primary efficacy analyses will be constructed to compare the primary endpoint between each dose regimen of fipaxalparant (HZN-825) and placebo, using the treatment policy strategy approach to intercurrent events. Details will be provided in the statistical analysis plan. All subjects who are randomized will be included in the primary efficacy analyses (ITT analysis set). The primary efficacy endpoint will be change from Baseline in FVC % predicted to Week 52. A mixed model for repeated measures (MMRM) will be fit to the data using observed change in FVC % predicted values from all planned post-Baseline assessments (Weeks 16, 28, 40 and 52) and including factors used for stratifying randomization as covariates (use of mycophenolate mofetil [yes/no] and presence of ILD [yes/no]). 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 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.

In the tipping point analysis, data from fipaxalparant (HZN-825) and placebo groups will be imputed under an Missing Not at Random (MNAR) assumption. The missing values in each treatment group will be imputed separately based on observed values in each group, respectively.

Then adjustments for each treatment group (placebo and fipaxalparant [HZN-825]) will be added to the imputed data and vary to find conditions with non-significant treatment effect. Sensitivity analyses will assess the use of rescue medication. The proportion of subjects who qualify for and who receive rescue medication at each potential time point will be summarized for each treatment group to determine whether there are different use rates between treatment groups. A sensitivity analysis will repeat the primary analysis except that it will ignore all FVC data collected after the initiation of rescue medication; the result will be a sensitivity analysis that uses a hypothetical strategy approach to the intercurrent event of initiation of rescue medication. A detailed plan for analyses, including how to handle the data impacted by COVID-19, will be provided in the statistical analysis plan.

9.6.4 Secondary Efficacy Endpoint Analyses

The key secondary endpoint for the trial will be change in mRSS from Baseline to Week 52. Analysis will follow that of the primary efficacy endpoint. Statistical significance on change in mRSS will only be concluded if statistical significance was achieved for the primary endpoint.

The proportion of subjects responding to treatment based on CRISS 25 will be evaluated using logistic model. The Revised CRISS (CRISS 25) is defined as improvement in at least 2 components: ≥5% increase for FVCpp 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.

The CGA, PTGA and Physical Effects and Physical Limitations subscales of the SSPRO-18 will be analyzed analogously to the primary efficacy endpoint.

The proportion of subjects with an mRSS decrease of ≥5 points and 25% from Baseline at Week 52 will be analyzed using a stratified analysis, with stratification by factors used for stratifying the randomization. Within each of the 4 resulting strata, data will be summarized and the strata will be combined into a single test statistic using Cochran-Mantel-Haenszel (CMH) weighting.

Components of the ACR-CRISS composite endpoint will be used to calculate the probability that a subject improved. If a subject does not have an event in Step 1 of the calculation and the equation in Step 2 shows a probability of at least 0.6 for an individual subject at Week 52, that subject will be classified as a responder; otherwise, the subject will be classified as a non-responder.

The predicted probability of improvement for each subject will be computed using the following equation in Step 2 (equation to derive predicted probabilities from a logistic regression model):

$$\frac{\exp(-5.54-0.81*\Delta MRSS+0.21*\Delta FVC\%-0.40*\Delta Pt-glob-0.44*\Delta MD-glob-3.41*\Delta HAQ-DI)}{1+\exp(-5.54-0.81*\Delta MRSS+0.21*\Delta FVC\%-0.40*\Delta Pt-glob-0.44*\Delta MD-glob-3.41*\Delta HAQ-DI)}$$

where Δ_{MRSS} indicates the change in mRSS from Baseline, $\Delta_{FVC\%}$ denotes the change in FVC% predicted from Baseline, $\Delta_{Pt\text{-}glob}$ indicates the change in PTGA, $\Delta_{MD\text{-}glob}$ denotes the change in CGA, and $\Delta_{HAQ\text{-}DI}$ is the change in HAQ-DI. All changes are absolute change ($Time_2$ – $Time_{baseline}$).

Analyses of ACR-CRISS and Revised CRISS (CRISS 25) response rates will be done using summary statistics and logistic models.

We will use NRI-MI (Non-Responder Imputation in conjunction with Multiple Imputation) for missing values observed in calculations of mRSS and ACR-CRISS responders at Week 52; and patients who died before Week 52 will be categorized as non-responders. This same rule will be applied to Revised CRISS (CRISS 25) analysis.

[redacted]

9.6.6 Safety and Tolerability Analyses

All subjects who receive at least 1 dose or partial dose of trial drug will be included in safety and tolerability analyses. Subjects who receive treatment other than that to which they were randomized will be included in summaries with the treatment received. Subjects who receive more than 1 treatment will be listed separately and included in summaries with the highest dose received. Supplemental analyses based on randomized dose groups for key safety analysis parameters if there are more than 5% patients with dose error in the trial.

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

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

Safety laboratory assessments (hematology and chemistry) and change from 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 Baseline to each visit will be summarized.

Descriptive summaries of observed and change from Baseline values will be presented for each vital sign parameter by visit. A shift table for vital signs by toxicity grade and visit will be summarized.

No inferential statistics are planned for any safety endpoint. But if needed, the exact methods may be used to evaluate AE/SAE risks for individual groups (i.e., QD, BID, and placebo) and difference between 2 groups (QD vs placebo, BID vs placebo).

9.6.7 Pharmacokinetic Analyses

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

[redacted]

9.6.9 Interim Analyses

After approximately 50% of the subjects reach Week 52 or discontinue the trial before Week 52, a futility analysis will be conducted using unblinded, comparative data. This analysis will have 2 potential outcomes:

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

The futility data will be reviewed by the IDMC. But the futility analysis will not be used to make a positive determination of efficacy to stop the trial.

Conditional power will be used to determine which of the options is chosen, with a conditional power of ≥10% required for at least 1 dose regimen to continue the trial.

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

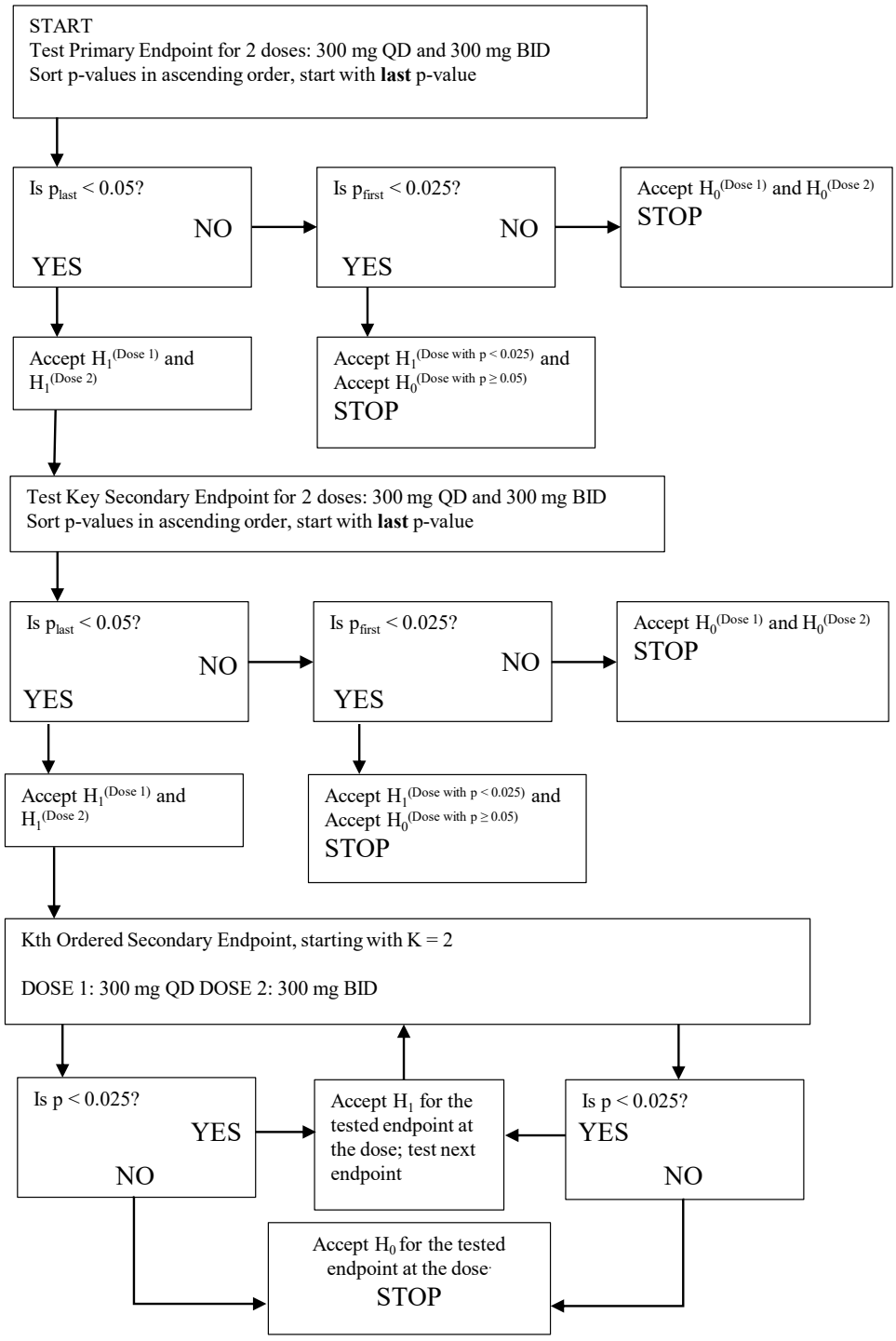
9.6.10 Multiple Comparisons

The overall statistical level is α=0.05 (2-sided).

Since 2 dose regimens of fipaxalparant (HZN-825) will be compared to placebo in the final analysis, adjustment for multiplicity will be used to preserve the family-wise error rate for multiple comparisons in the primary analysis. For the primary endpoint change from Baseline in FVC % predicted at Week 52, a Hochberg testing procedure will be used for the comparisons of fipaxalparant (HZN-825) BID vs. placebo and fipaxalparant (HZN-825) QD vs placebo. The resulting p-values will be ranked, and the larger p-value will be evaluated at the $\alpha = 0.05$ (2-sided) threshold. If statistically significant, then both comparisons will be considered significant. If the larger of the two P-values is not statistically significant at $\alpha = 0.05$ (2-sided), then the smaller P-value will be compared to an $\alpha = 0.025$ (2-sided).

If 1 or both dose regimens of the primary endpoint are not rejected after completing testing, no further testing will occur due to exhaustion of all alpha. If both fipaxalparant (HZN-825) doses are statistically significantly better than the placebo for the primary efficacy endpoint at $\alpha=0.05$ (2-sided), the same Hochberg testing procedure will subsequently be used to evaluate the key secondary endpoint. If both dose regimens of fipaxalparant (HZN-825) for the key secondary endpoint are considered significant, subsequent secondary endpoints will be tested sequentially within each dose in the order shown in Section 9.6.1.2, using $\alpha=0.025$ (2-sided) in a sequential testing procedure. If all preceding sequentially tested hypotheses are rejected at $\alpha=0.025$ (2-sided), the next hypothesis will be tested. Once a hypothesis is not rejected, all subsequent endpoints within the same dose will not be tested due to alpha exhaustion. A graphic representation of the proposed multiplicity testing approach is presented in Figure 9.2.

Figure 9.2 Schematic of Hochberg Testing Procedure



9.6.11 Sample Size and Power Considerations

Based on prior trials of tocilizumab [Khanna and Denton et al., 2016; Khanna and Lin et al., 2020] and abatacept [Khanna and Spino et al., 2020] in a similar subject population, change in FVC % predicted is expected to have a standard deviation of 8 to 8.5 percentage points after 52 weeks of treatment. Assuming a clinically important difference between fipaxalparant (HZN-825) and placebo of 4 percentage points and a standard deviation of 8.5, a sample size of 100 subjects per treatment group will provide 85% power to demonstrate an improvement between a dose regimen of fipaxalparant (HZN-825) and placebo using α=0.025, 2-sided.

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, electroencephalogram, radiology, pathology and special assessment reports; dispensing records; signed ICFs; consultant letters; and subject Screening and enrollment logs.

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

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

11 CASE REPORT FORMS

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

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

12 TRIAL MONITORING

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

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

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

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

At intervals during the trial, as well as after the completion of subject enrollment, the trial center will be monitored by the Sponsor or designee for compliance. During these visits, the monitor will discuss trial progress, verify adherence to the protocol and the completeness, consistency and accuracy of the data being entered on the eCRF (source data verification); oversee the resolution of outstanding data discrepancies; and check on various aspects of trial conduct (e.g., drug accountability, sample storage). The Investigator agrees to allow 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 (eg 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.

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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]

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:_____

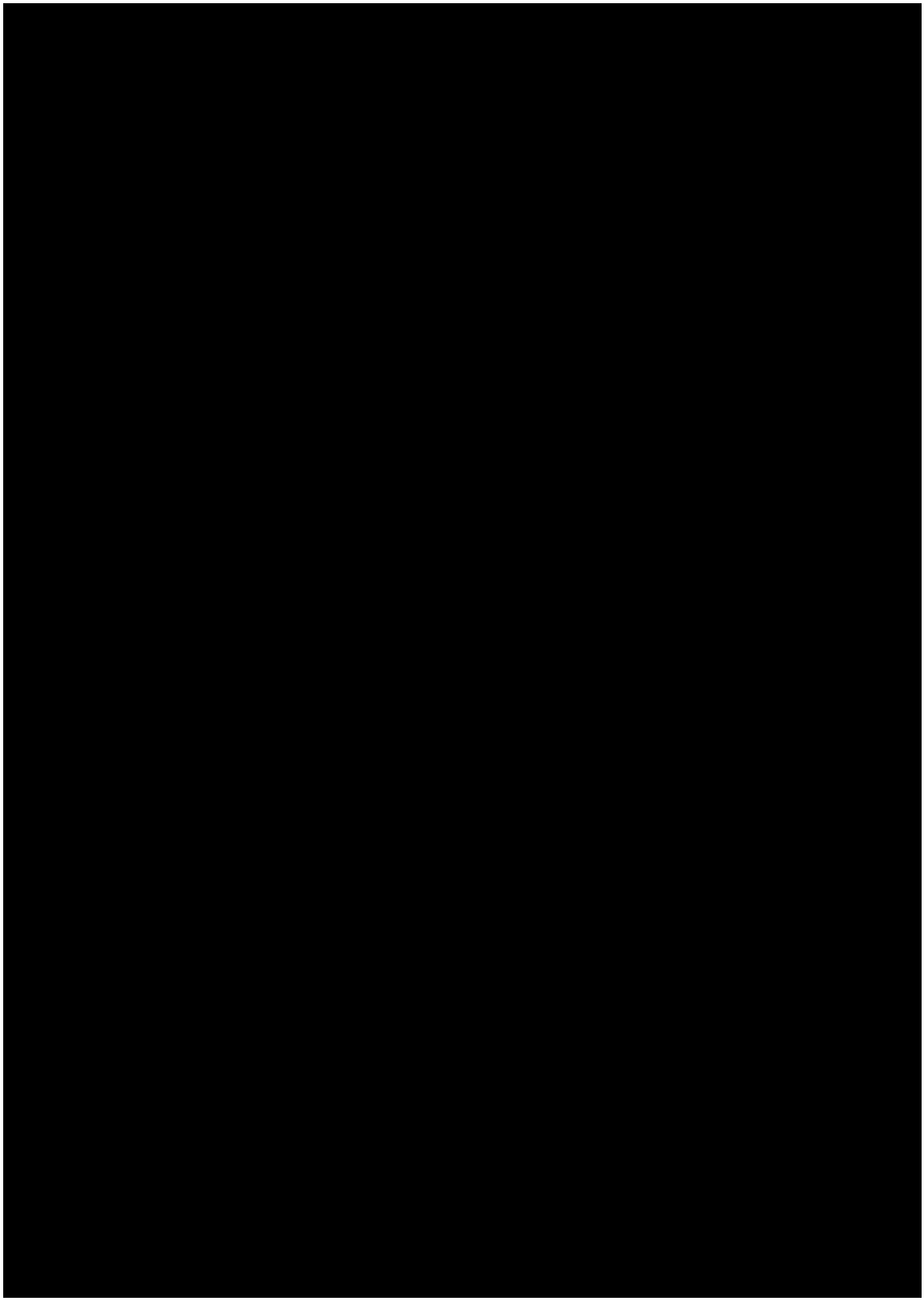
_____

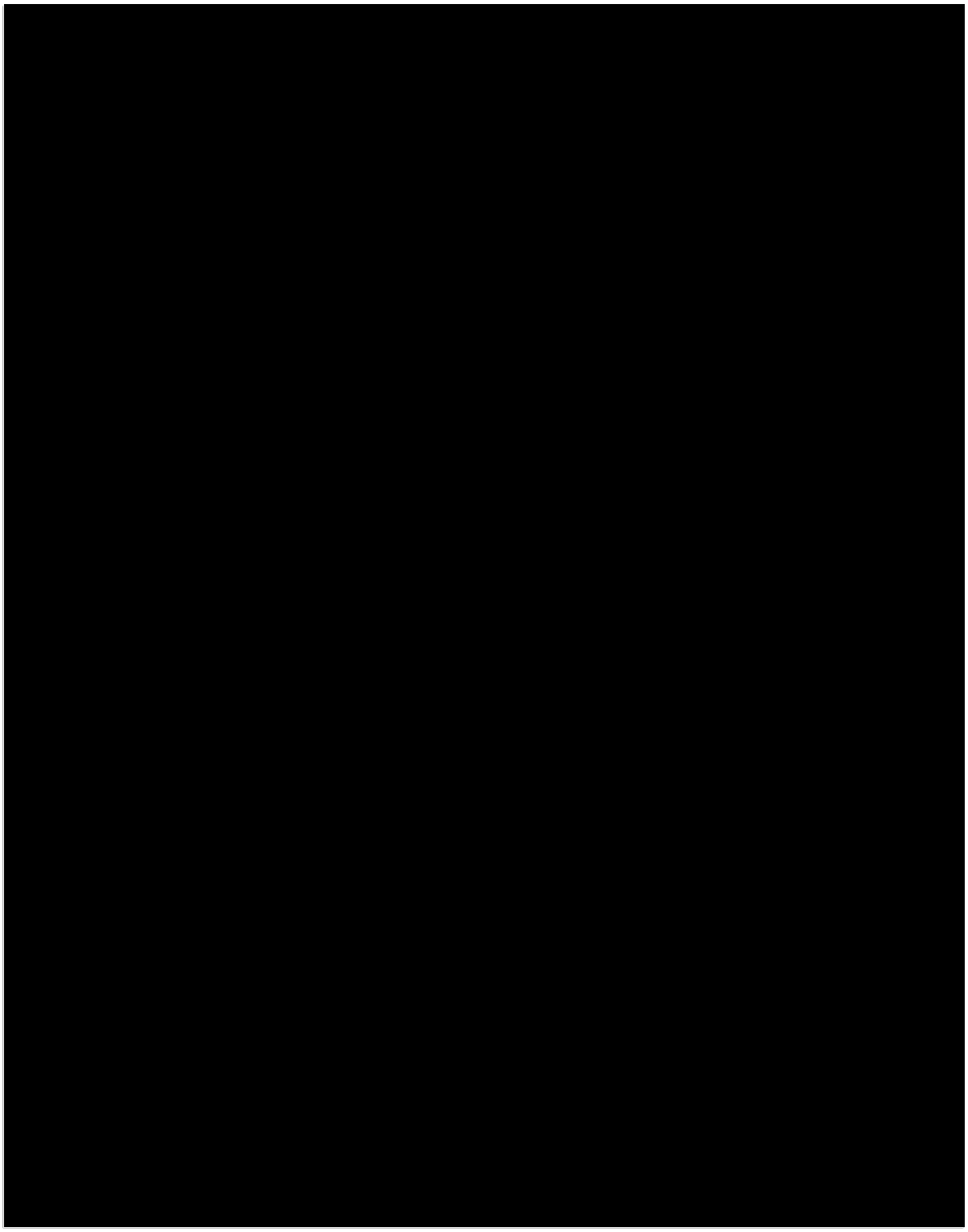
_____

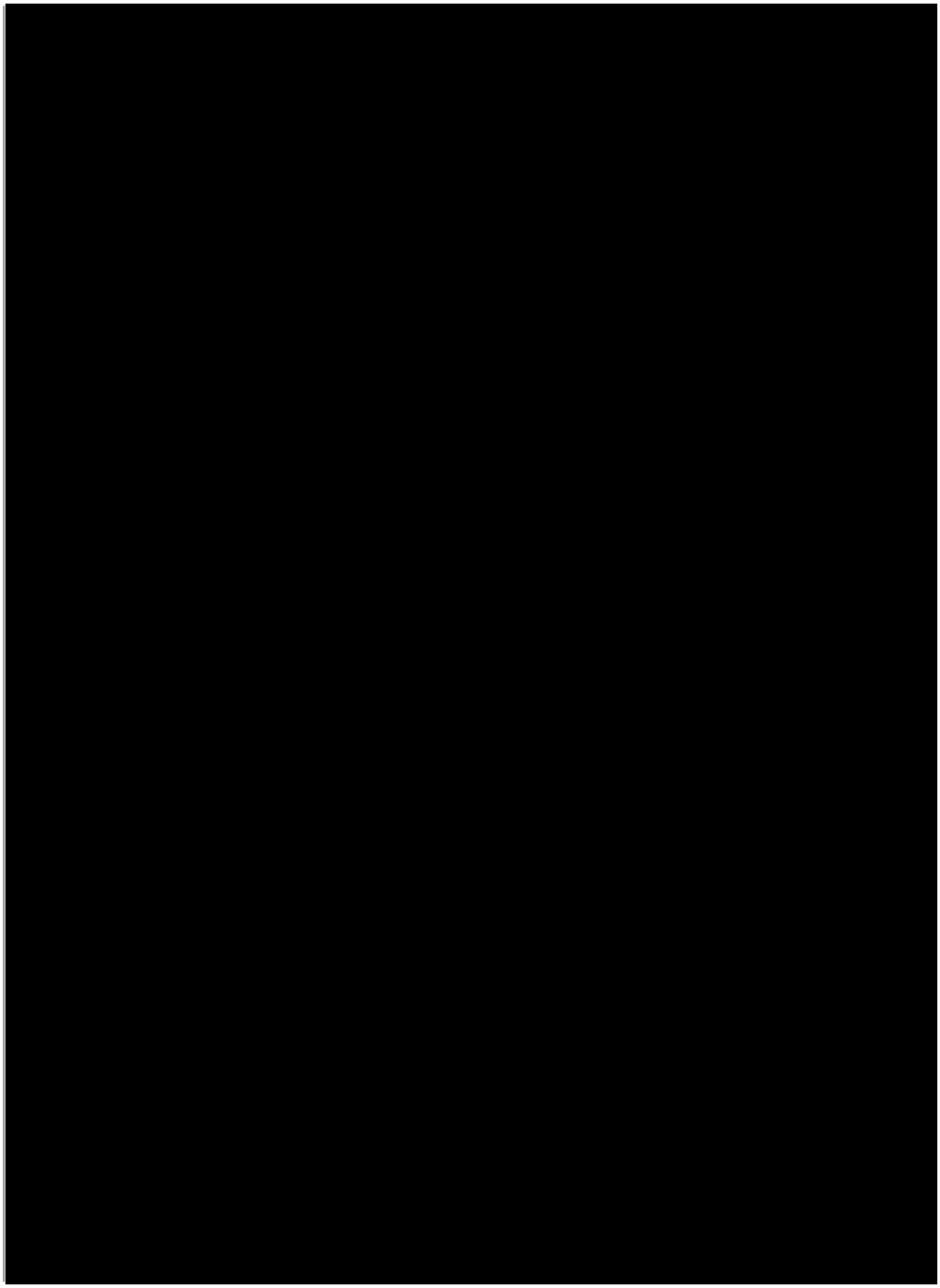
B4. Sum the 17 area scores for the Total mRSS score: ☐☐

Assessors Signature: _____

Source: Khanna et al., 2017







17.5 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										Extremely poor
0. ☐	1. ☐	2. ☐	3. ☐	4. ☐	5. ☐	6. ☐	7. ☐	8. ☐	9. ☐	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										Severe pain
0. ☐	1. ☐	2. ☐	3. ☐	4. ☐	5. ☐	6. ☐	7. ☐	8. ☐	9. ☐	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										Very severe limitation
0. ☐	1. ☐	2. ☐	3. ☐	4. ☐	5. ☐	6. ☐	7. ☐	8. ☐	9. ☐	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										Extremely active
0. ☐	1. ☐	2. ☐	3. ☐	4. ☐	5. ☐	6. ☐	7. ☐	8. ☐	9. ☐	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.

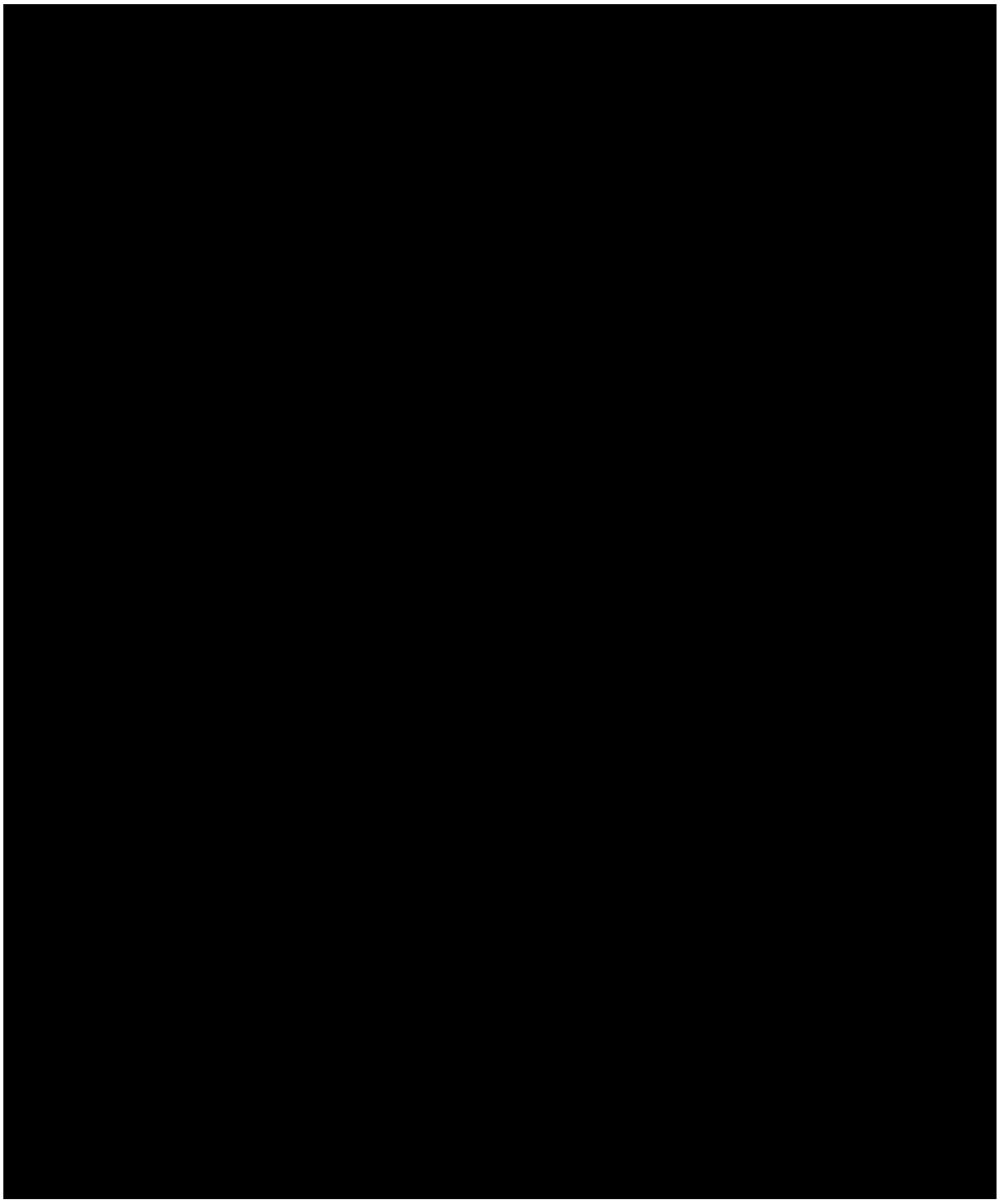
Over the PAST 4 WEEKS:	Not at all → Very Much
1. How tight has your skin felt?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
2. How dry has your skin been?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
3. How painful has your skin been?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
4. How discolored has your skin been?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
5. How itchy has your skin felt?	☐0 ☐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

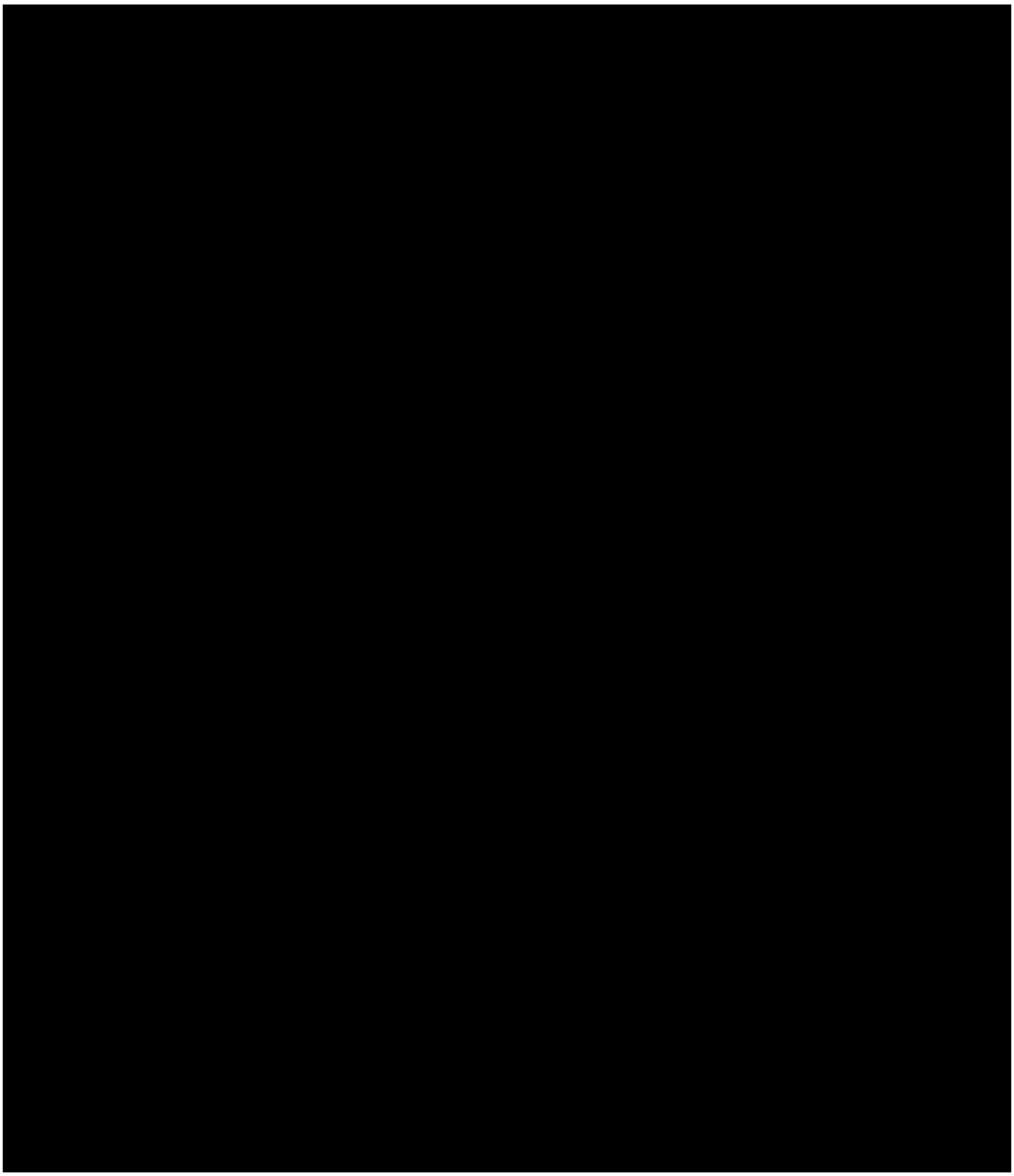
Version: November 2017

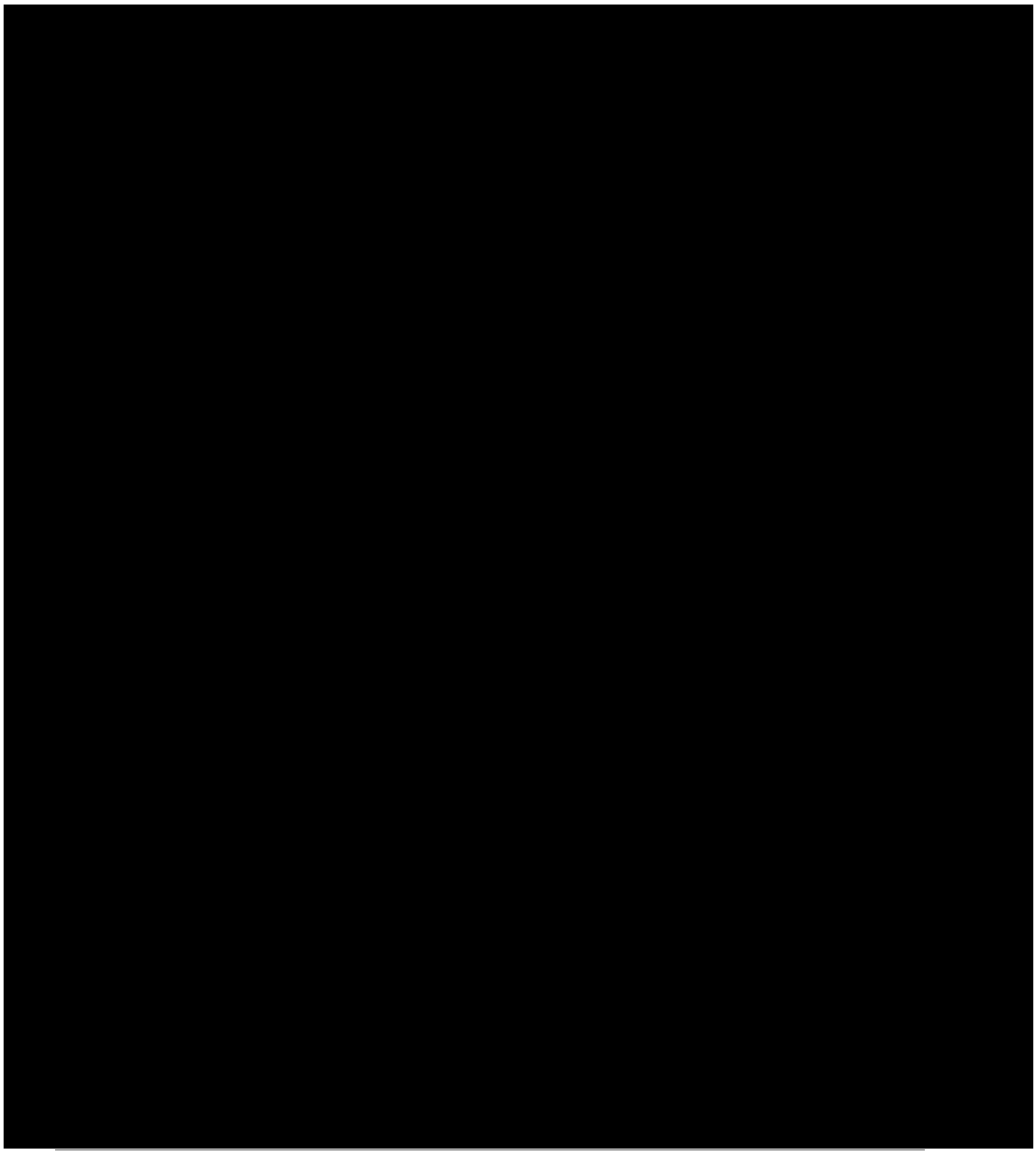
SCLERODERMA SKIN PATIENT REPORTED OUTCOME (SSPRO)

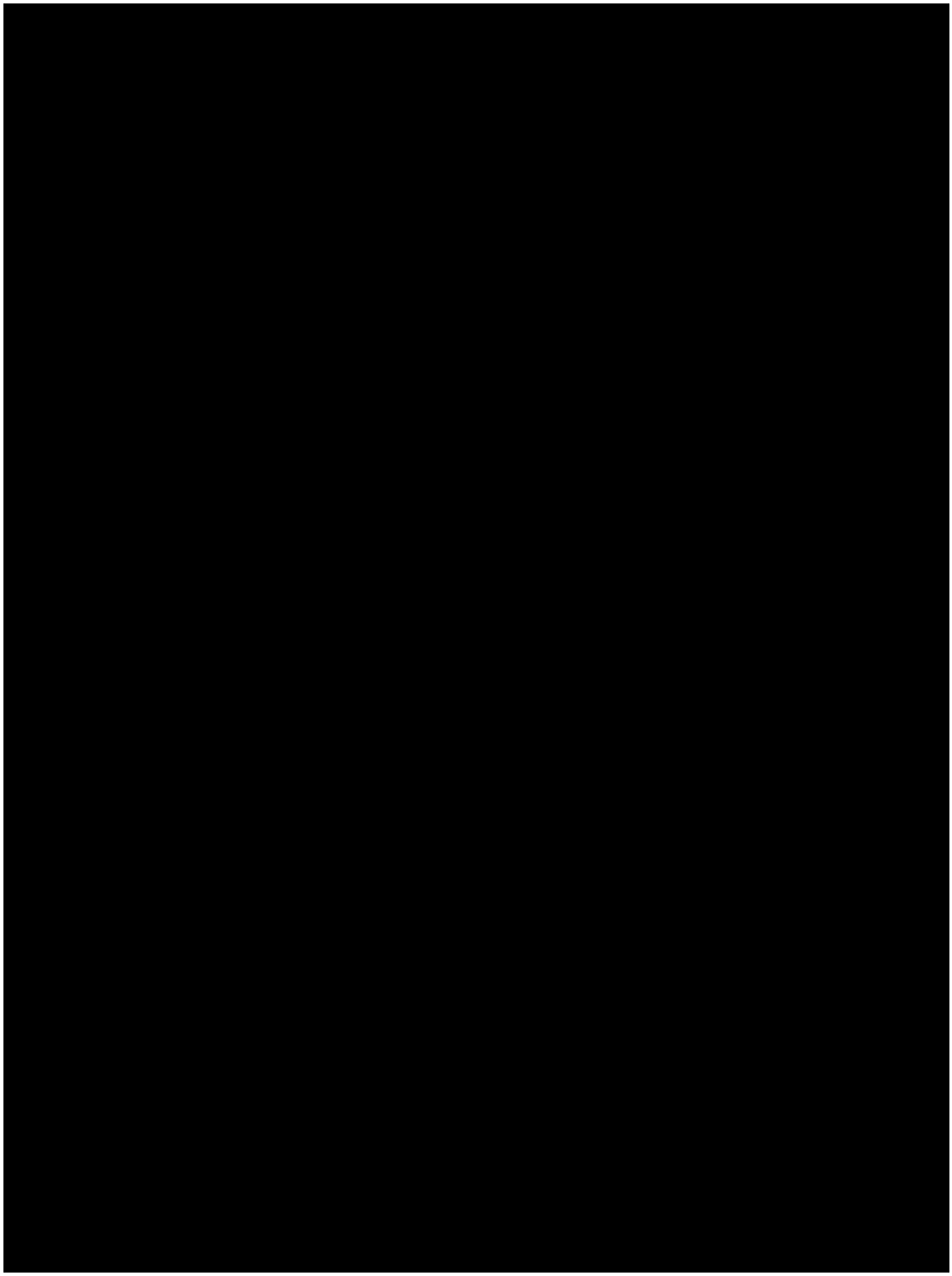
12. How much difficulty have you had **doing things with your hands** because of skin tightness?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
13. How much difficulty have you had with **opening or closing your mouth** because of skin tightness?	☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6
14. How much difficulty have you had with **moving parts of 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

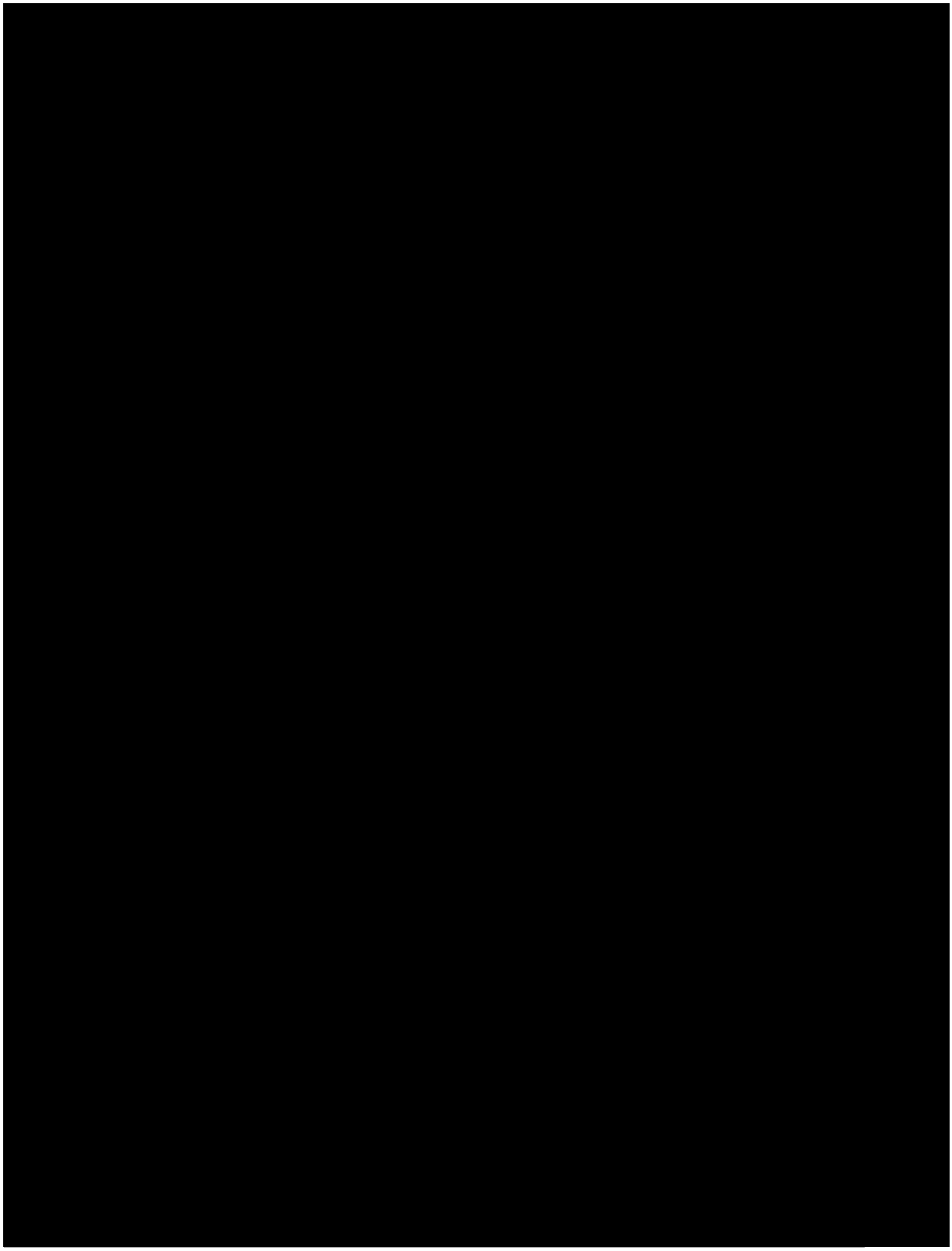
Version: November 2017

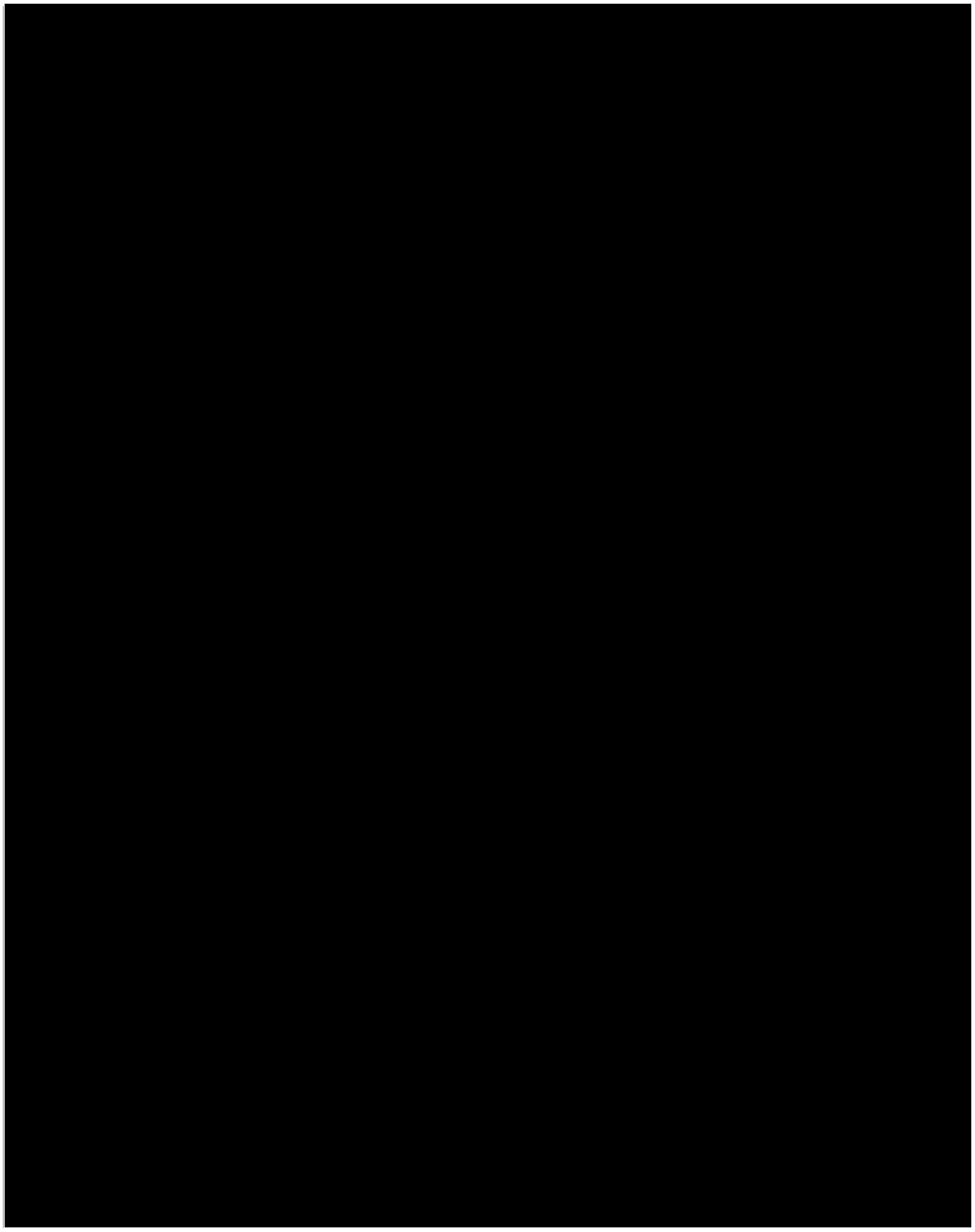


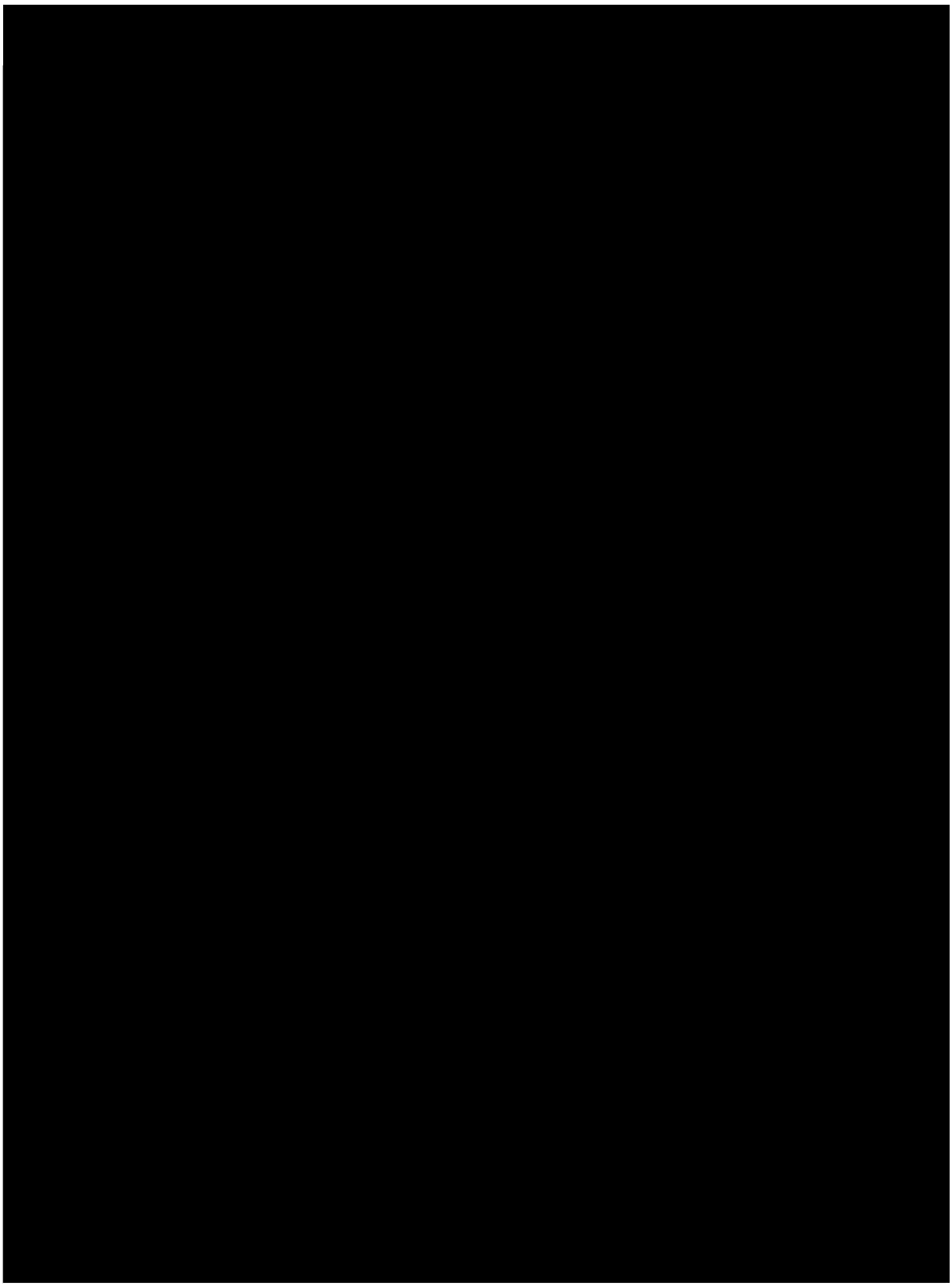


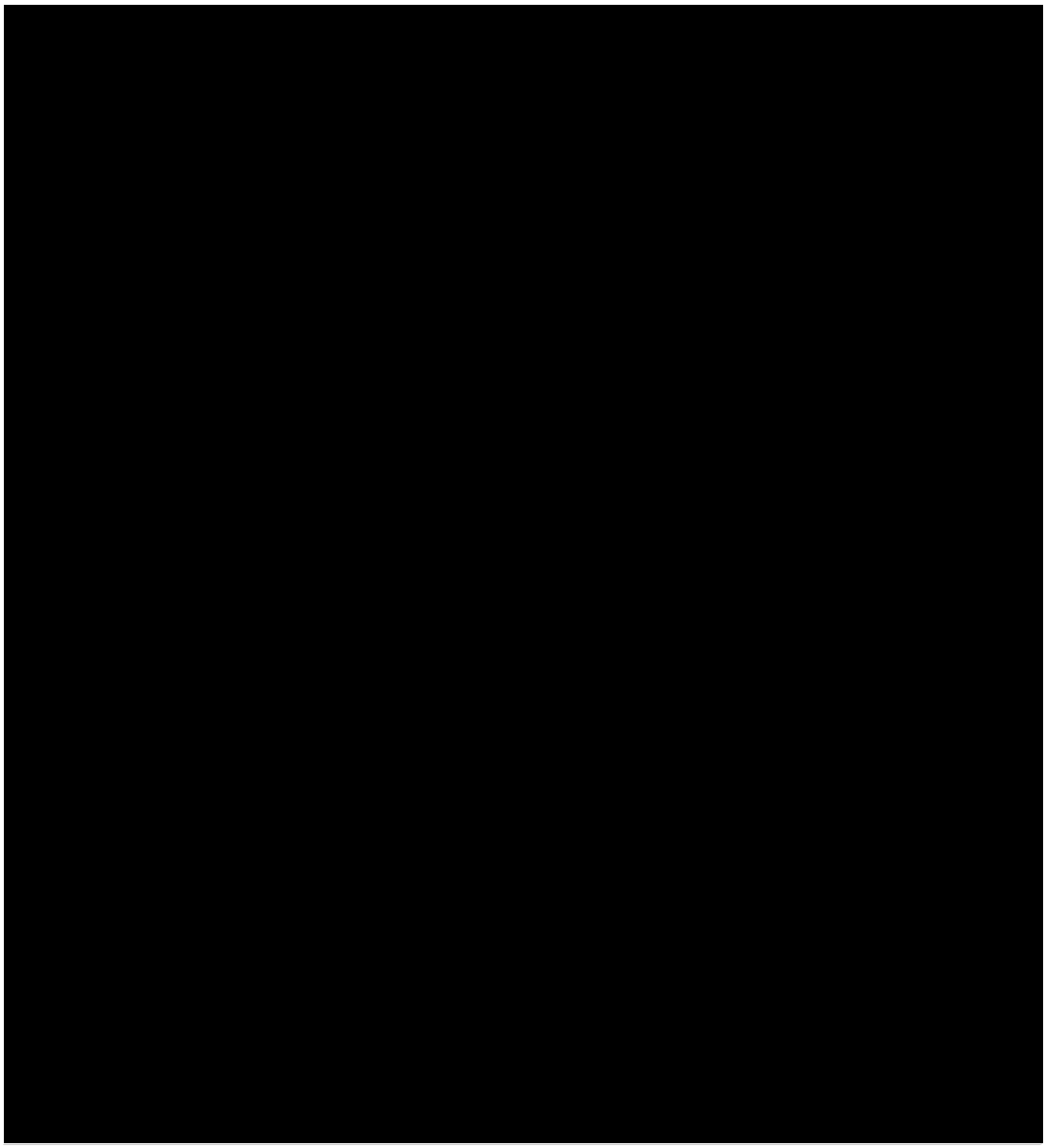


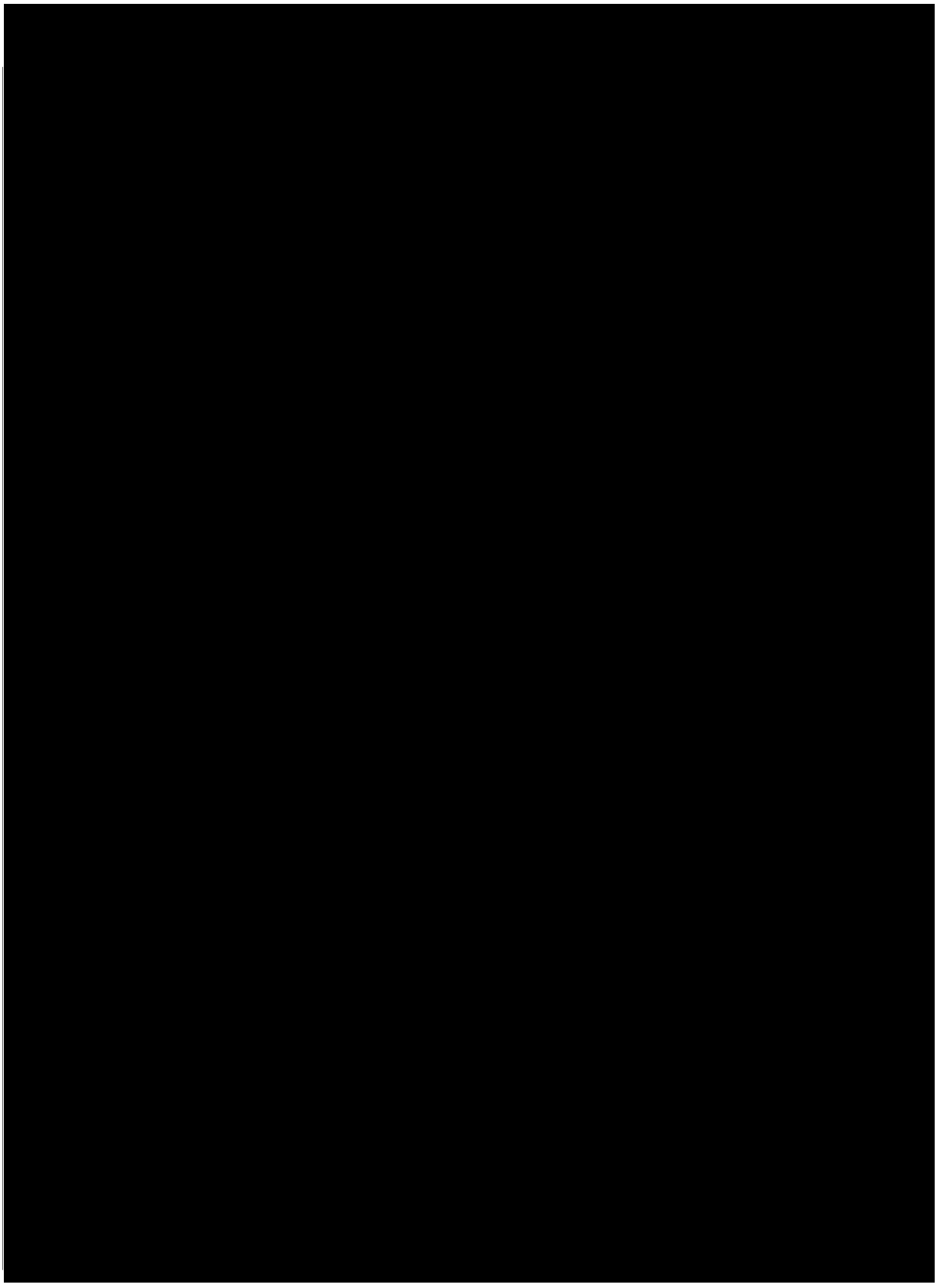












17.13 Serious Adverse Events Anticipated in the Trial Population

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 9.5.4.1.1.2 (Serious Adverse Event Definition). The Investigator is required to follow the requirements detailed in Section 9.5.4.1.5 (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 with placebo, an expedited IND safety report may be submitted to the FDA.

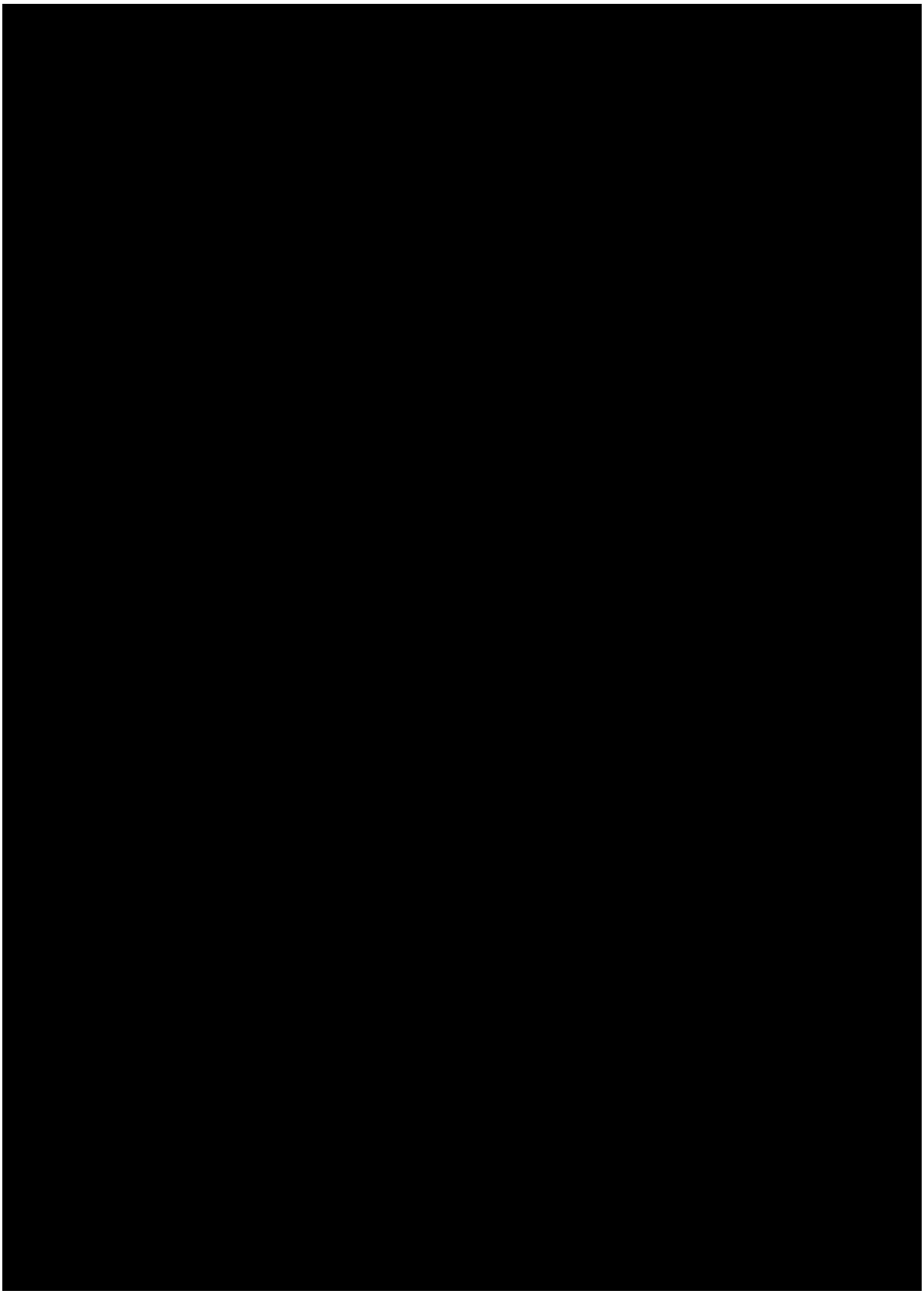
Renal system: scleroderma renal crisis (refer to Section 9.5.1.1 for the definition), accelerated hypertension

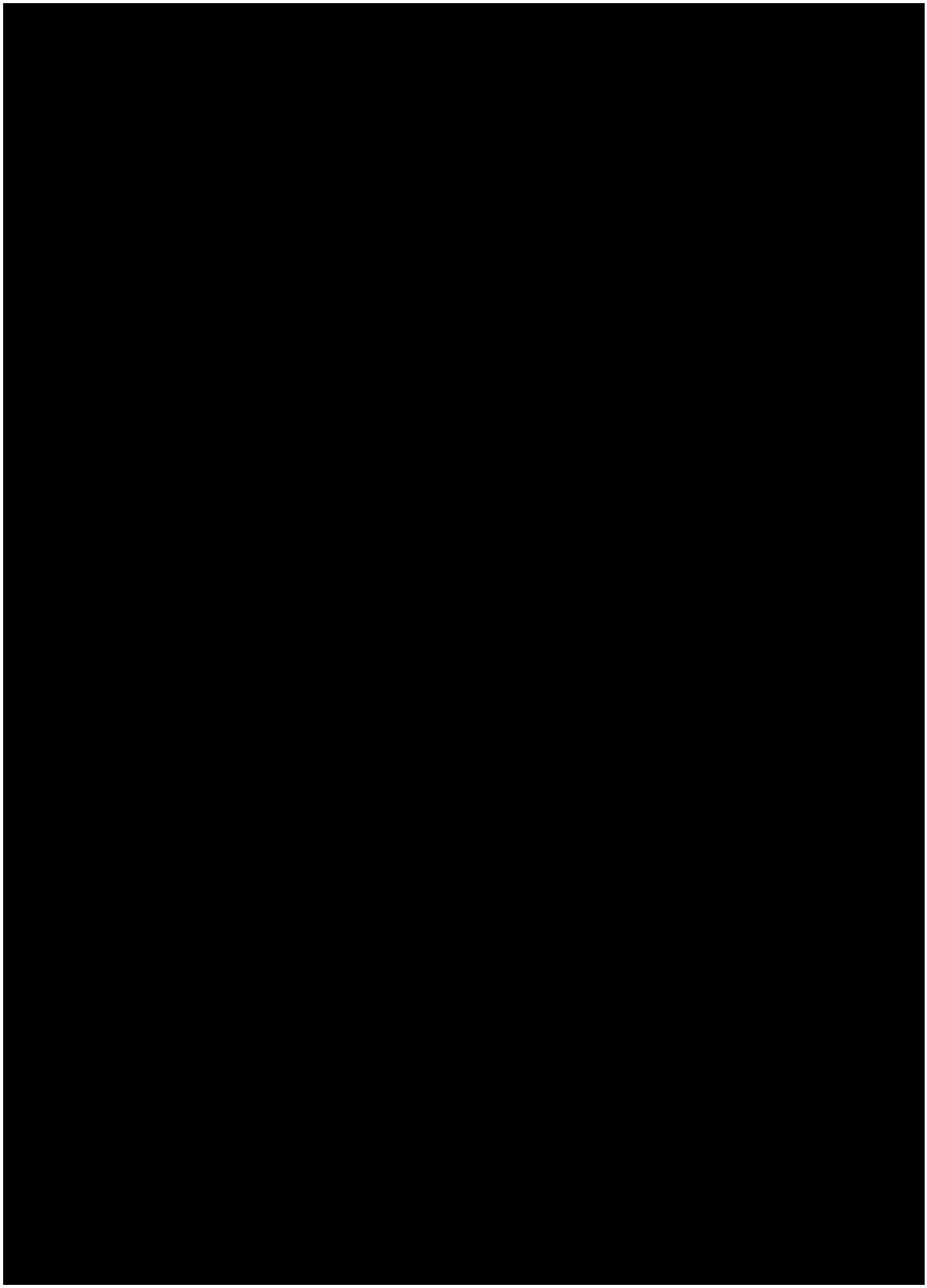
Cardiovascular system: cardiac failure (including acute, chronic and congestive), ventricular failure (including ejection fraction decreased), pericardial effusion, pericarditis, supraventricular tachyarrhythmia, hypotension

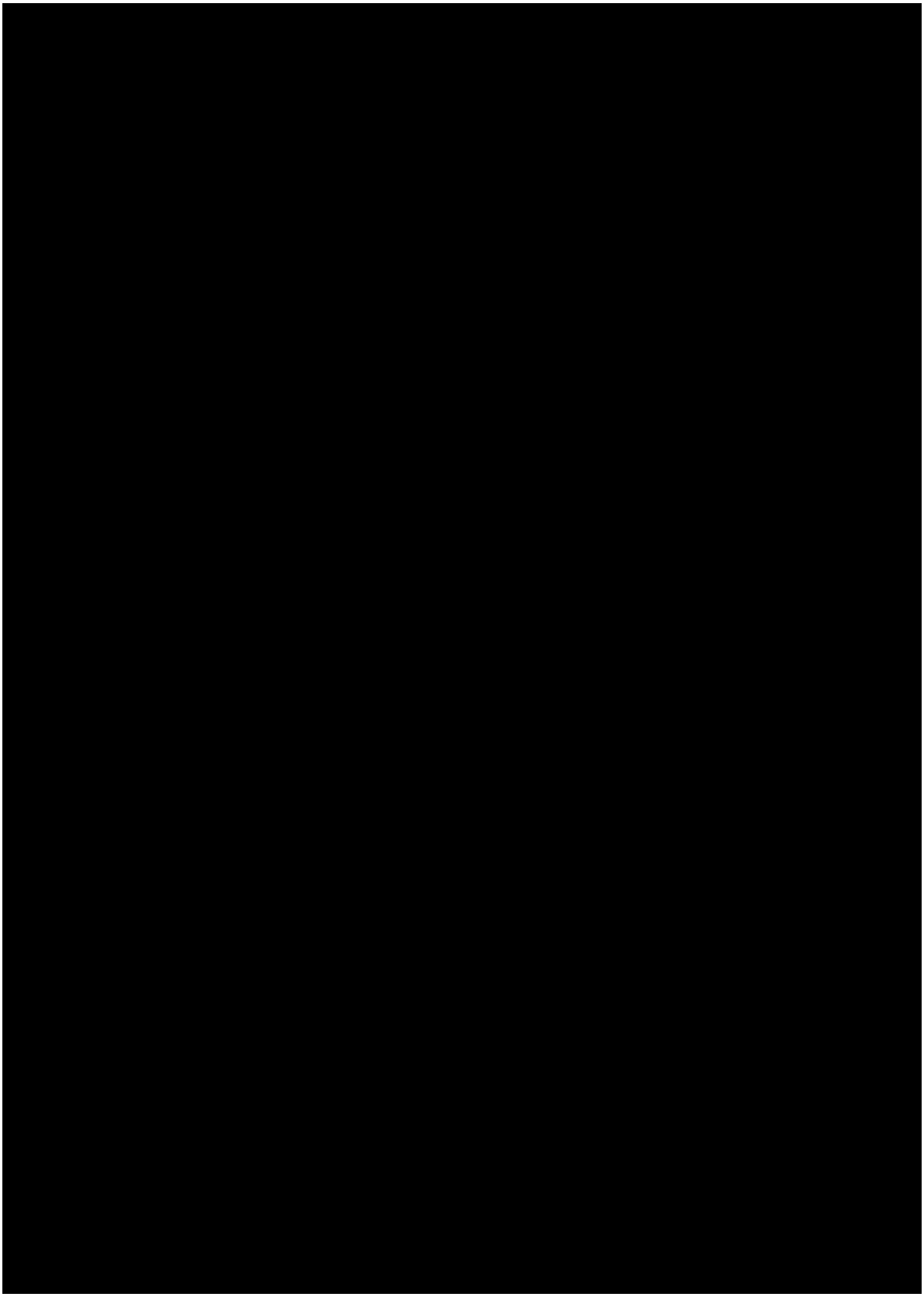
Pulmonary system: pulmonary arterial hypertension, pulmonary hypertension, forced vital capacity decreased, interstitial lung disease

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

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







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 total bilirubin (TBL) >2 × ULN should be followed by repeat testing (ALT, AST, ALP, 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

Document Name: Protocol Amendment fipaxalparant 20230130 4

Document Description: HZNP-HZN-825-301 v5.0 Protocol Amendment 4

Document Number: CLIN-000346537

Approval Date: 23 Aug 2024

Type of Study Protocol: Amendment

Protocol Amendment No.: 4

Document Approvals	
Reason for Signing: Management	Name: [redacted] Date of Signature: 23-Aug-2024 17:40:00 GMT+0000

SUMMARY OF CHANGES
Protocol HZNP-HZN-825-301
Version 3.0 Amendment 2, incorporating Protocol Version 2.0 and Protocol Version 2.1
(protocol amendment for the United Kingdom)

Key additions, revisions and clarifications to Version 2.0 of the protocol are:

- Updating the Sponsor's address.
- [redacted]
- Updating the primary analysis set definition (i.e., changing the primary analysis set from the intent-to-treat analysis set to the full analysis set).
- Clarifying that the [redacted] can be taken from affected or unaffected skin in the forearm and that this requirement is applicable to the first 110 subjects.
- Highlighting that [redacted] collection can occur anytime during Screening prior to the first dose of trial drug.
- Clarifying that the coagulation profile should be assessed before [redacted] if the [redacted] is performed during Screening.
- Including further guidance about acceptable use of restricted medications as part of the entry criteria evaluation in exclusion criterion 9.
- Adding new requirements around condom use and aligning text with Section 9.5.4.2 in exclusion criterion 13.
- Clarifying the definition of active hepatitis B and reformatting exclusion criterion 18 for clarity.
- Updating the multiplicity handling approach to the Hochberg method.
- 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.
- Including restricted medication use as a specific reason for discontinuation from trial treatment.
- 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).
- Including some additional cautions around use of specific concomitant medications.
- [redacted]

- Deleting mention of subject (i.e., exit) interviews from the schedule of assessments and clarifying that they will be covered by a separate protocol.
- Adding the definition of a suspected adverse reaction.
- Clarifying documentation and reporting for medication errors.
- Adding clarification around abstinence as a contraceptive method.
- Allowing subject visits to be performed at locations other than the trial site.
- Alerting trial personnel that the actual assessment instruments used may differ from those in Section 17 of the protocol.
- [redacted]
- [redacted]

Minor wording changes and correction of minor typographical errors are not detailed below.

SUMMARY OF CHANGES
Protocol HZNP-HZN-825-301
Version 2.0 Amendment 1, incorporating Protocol Version 1.0, Administrative Change 1, Amendment 1.1 (protocol amendment for France) and Version 1.0 Addenda for Germany/Austria, Italy, Portugal and Spain

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

- Changing the Medical Monitor to [redacted], MD.
- [redacted]
- In inclusion criterion 4, matching the accepted disease definition of diffuse cutaneous systemic sclerosis and aligning with the criterion described in the referenced publication.
- Removed inclusion criterion 6 to focus solely on patients with early disease and significant skin involvement (mRSS 15 or higher).
- Removed inclusion criterion 7 to remove the elevated acute phase reactants criteria since patients are allowed to enter the study with protocol-specified, stable, concomitant immunosuppression.
- Updating the development phase of the trial from 2b/3 to 2b.
- To minimize the amount of missing data, emphasizing that subjects who prematurely discontinue trial drug will be asked to remain in the trial, participating in the scheduled trial visits through Week 52.
- Excluding subjects with moderate to severe hepatic impairment.
- Adding a physical examination at Week 28 and clarifying the assessments (cardiac, pulmonary, neurologic, skin and directed rheumatology assessments) to be included as part of the physical examination.
- Specifying that subjects should be fasting for the Day 1, Week 28 and Week 52/End of Treatment/Premature Discontinuation Visits.
- Changing the blood sample collection for lipid profile to occur at Screening and the Day 1, Week 28 (was Week 16 in version 1.0 of the protocol) and Week 52/End of Treatment/Premature Discontinuation Visits.
- Specifying that erythrocyte sedimentation rate must be processed within 1 hour of the blood collection for hematology.
- Allowing for an echocardiogram that has been performed within the 3 months prior to Baseline to serve as the Baseline echocardiogram if the subject has been clinically stable.
- Updating nonclinical information pertaining to $LPAR_1$ and HZN-825 nonclinical pharmacology as it pertains to lung fibrosis.
- Updating clinical data to be current as of 10 January 2021.

- Adding a section on the assessment of benefits and risks of HZN-825 treatment.
- Specifying that trial drug should be taken with a meal to achieve sufficient targeted drug exposure.
- Updating various sections for consistency with the electronic case report form (eCRF), other HZN-825 protocols and/or the Investigator's Brochure.
- Clarifying that, prior to any site closure, discussion should occur among the site Principal Investigator, Medical Monitor, Trial Manager and possibly the Site Monitor.
- Clarifying how missed doses of trial drug should be handled.
- Adding cyclosporine, organic anion transporter polypeptide (OATP) inhibitors, P-glycoprotein (P-gp) inhibitors and a breast cancer resistance protein (BRCP) inhibitor as restricted medications.
- Adding international normalized ratio (INR) monitoring when warfarin is used, since HZN-825 is a very weak cytochrome P450 (CYP)2C9 inhibitor.
- Emphasizing that, even for deterioration, the methotrexate dosage must be ≤15 mg/week.
- Clarifying that the first dose of trial drug on Day 1 and the morning dose of trial drug at the Week 16 and Week 28 Visits are to be taken in the clinic (i.e., visits with post-dose pharmacokinetic samples).
- Adding definitions of women of childbearing potential (WOCBP), postmenopausal women and fertile men to exclusion criterion 13.
- Changing pregnancy testing to every 4 weeks and adding examples of highly effective contraceptive methods.
- Adding a statement that development safety update reports will be submitted to countries and territories as required.
- Adding the definition of "end-of-trial."
- Clarifying that unblinded information will be restricted from Horizon trial team members who are involved in all aspects of trial conduct and management.
- Providing guidance regarding restarting trial drug after a subject experiences clinically significant [redacted].
- Providing regional addresses for the central safety laboratory.
- Removing long-term survival follow-up.
- Clarifying serious adverse event (SAE) reporting requirements.
- Adding reasons that a treatment group or the trial may be discontinued.
- Indicating Investigator discretion in repeat of spirometry prior to rescue medication.
- Clarifying that azathioprine and cyclophosphamide are not permitted for 4 weeks prior to Screening and throughout Screening.
- Adding a section on echocardiogram for consistency with other HZN-825 protocols.

- Specifying collection of a fasting blood sample for lipid profile in Section 9.5.6 (Trial Procedures) at Day 1, Week 28 and Week 52/End of Treatment/Premature Discontinuation for consistency with the Schedule of Assessments.

Minor wording changes and correction of minor typographical errors are not detailed below.