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STATISTICAL ANALYSIS PLAN (SAP)

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

Study Number:	**HZNP-HZN-825-302**
Study Product:	**HZN-825**
Development Phase:	Phase 2b
Sponsor:	Horizon Therapeutics Ireland DAC 70 St. Stephen's Green Dublin 2 D02 E2X4 Ireland
Version:	1.0
Version Date:	11Jan2024
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Council for Harmonisation) and all applicable national and local regulations.

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1 Revision History and Approvals

Version	Effective Date	Author	Summary of Change
1.0	11Jan2024	[redacted]	Initial Version

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2 List of Abbreviations

Abbreviation	Definition
ACR-CRISS	American College of Rheumatology-Composite Response Index in Systemic Sclerosis
AE	adverse events
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BID	twice daily
COVID-19	Coronavirus disease of 2019
CS	clinically significant
CSR	clinical study report
CV%	coefficient of variation
DBL	database lock
DLCO	diffusing capacity of the lungs for carbon monoxide
DRM	data review meeting
EAIR	event adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
FAS	full analysis set
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FCS	fully conditional specification
FVC %	forced vial capacity percent
GIT	gastrointestinal tract
HAQ-DI	Health Assessment Questionnaire - Disability Index
HRCT	high-resolution computed tomography
hsCRP	high sensitivity C-reactive Protein
ICE	intercurrent event
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IDMC	independent data monitoring committee
ILD	interstitial lung disease
IVRS	interactive voice response system

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Abbreviation	Definition
LPAR1	lysophosphatidic acid receptor 1
ITT	intention-to-treat
LS	least squares
MAR	missing at random
MCS	mental component score
MDGA	Physician Global Assessment
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
MMRM	mixed model repeated measures
mRSS	modified Rodnan skin score
NCS	not clinically significant
PAH	pulmonary hypertension
PCS	physical component score
PD	protocol deviation
PK	pharmacokinetics
PMM	pattern mixture model
PP	per-protocol
PT	preferred term
PTGA	Patient Global Assessment
PYE	person years of exposure
Q1	first quartile
Q3	third quartile
QD	once daily
RCTC	rheumatology common toxicity criteria
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SD	standard deviation
SF-12	SF-12® Health Survey
SHAQ	Scleroderma Health Assessment Questionnaire
SI	International System of Units
SMQ	standard MedDRA query
SOC	system organ class
SSc	systemic sclerosis

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Abbreviation	Definition
SSC GIT	scleroderma gastrointestinal tract
SScQoL	Systemic Sclerosis Quality of Life Questionnaire
SSPRO-18	scleroderma skin patient-reported outcome
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
UCLA SCTC GIT	University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract
VAS	visual assessment scale
WHO	World Health Organization

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3 Purpose

This SAP provides a detailed and complete description of the planned statistical analyses of the study HZNP-HNZ-825-302 to support the Clinical Study Report (CSR).

This SAP complies with the International Council for Harmonization (ICH) E9 'Statistical Principles for Clinical Trials' and E9(R1) 'Statistical Principles for Clinical Trials: Addendum on Estimands and Sensitivity Analysis in Clinical Trials', and is based upon the following study documents:

- Clinical Study Protocol Version 2.2 (dated 04 January 2024)
- electronic Case Report Form (eCRF), Version 2292 (dated 17 MAR 2023)

All decisions regarding the final analysis of the study results, as defined in this SAP, have been made before database lock (DBL) of the study data.

Deviations from the analyses in this SAP will be detailed in the CSR.

4 Study Design

This is an open-label, repeat-dose, multicenter extension trial of HZNP-HZN-825-301.

Subjects who complete the double-blind Treatment Period (Week 52) in Trial HZNP-HZN-825-301 will be eligible to enter this 52-week extension trial. Subjects who entering this extension trial will complete the Week 52 Visit activities in HZNP-HZN-825-301 and will not complete the Safety Follow-up Visit 4 weeks after the last dose of trial drug in HZNP-HZN-825-301.

On Day 1 (Week 52 Visit of HZNP-HZN-825-301), subjects will receive their first dose of HZN-825 in this extension trial at the clinic and will participate in trial visits at Week 4 and every 6 weeks thereafter until Week 52. The Week 52 Visit activities in HZNP-HZN-825-301 will serve as Trial Baseline for this extension trial.

If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 52. If a subject prematurely discontinues trial drug and does not wish to continue in the trial, he/she will return for a clinic visit and undergo the Week 52 assessments. Subjects will participate in a Safety Follow-up Visit 4 weeks after the last dose of HZN-825.

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

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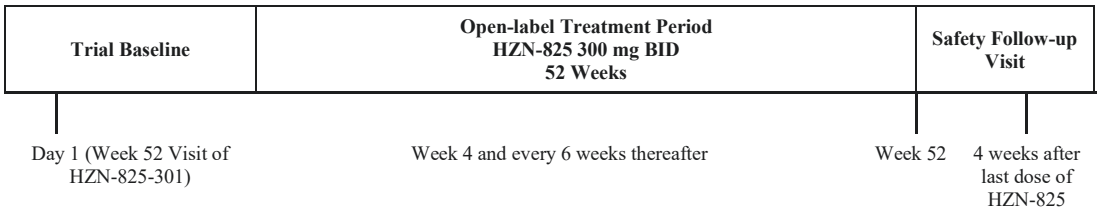
Figure 1 Schematic of Trial Design



4.1 Objectives and Endpoints

The overall objective is to investigate the efficacy, safety, and tolerability of HZN-825, a selective antagonist of lysophosphatidic acid receptor 1 (LPAR1), administered 300 mg BID to subjects with diffuse cutaneous systemic sclerosis (SSc) in a 52-week open-label extension following completion of the randomized, double-blind, 52-week clinical trial (HZNP-HZN-825-301). There are two types of Baseline (Trial Baseline and HZN-825 Baseline) used in analyses.

There are two types of Baselines that are defined in this open-label extension trial:

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

4.1.1 Primary Objective

The primary efficacy objective is to assess the efficacy of 52 weeks of open-label treatment with HZN-825 in subjects with diffuse cutaneous SSc, as measured by change from both Baselines in forced vial capacity percent (FVC %) predicted.

The primary safety objective is to examine the safety and tolerability of 52 weeks of open-label treatment with HZN-825, inclusive of, but not limited to, adverse events (AEs), serious adverse events (SAEs) and the adverse event of special interest (AESI), from Day 1 to 4 weeks after last dose.

4.1.2 Exploratory Objectives

The exploratory objectives are to evaluate the following after 52 weeks of open-label treatment with HZN-825.

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4.1.3 Exploratory Efficacy Endpoints:

1. Evaluate the effect on change from both Baselines in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 52.
2. Evaluate the effect on Physician Global Assessment (MDGA) for change from both Baselines. at Week 52
3. Evaluate the effect on Patient Global Assessment (PTGA) for change from both Baselines at Week 52.
4. Evaluate the effect on the Physical Effects subscale of the scleroderma skin patient-reported outcome (SSPRO-18) for change from both Baselines at Week 52.
5. Evaluate the effect on the Physical Limitations subscale of the SSPRO-18 for change from both Baselines at Week 52.
6. Proportion of subjects with a modified Rodnan skin score (mRSS) decrease of >=5 points and 25% from both Baselines at Week 52.
7. Responder rate, defined as American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS) predicted probability of at least 0.6, improvement from both Baselines at Week 52.
8. Proportion of subjects with an improvement in ≥3 of 5 core measures from both Baselines: ≥20% in mRSS, ≥20% in HAQ-DI, ≥20% in PTGA, ≥20% in MDGA and ≥5% in FVC % predicted at Week 52 (ACR-CRISS-20).
9. Evaluate the effect on the SSPRO-18 for change from both Baselines at Week 52.
10. Evaluate the effect on University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) for each scale and the total GIT score change from both Baselines at Week 52.
11. Evaluate the effect on Raynaud's phenomenon using the Raynaud's Assessment for change from both Baselines at Week 52.
12. Evaluate the effect on Scleroderma Health Assessment Questionnaire (SHAQ) for change from both Baselines at Week 52.
13. Evaluate the effect on change from both Baselines in Systemic Sclerosis Quality of Life Questionnaire (SscQoL) scores at Week 52.
14. Evaluate the effect on change from both Baselines in SF-12® Health Survey (SF-12) scores at Week 52.

15. Evaluate the effect on change from both Baselines in pain and pain component scale scores at Week 52
16. Evaluate the effect on change from both Baselines in fatigue based on Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F) score at Week 52.
17. Evaluate the change from both Baselines in the mRSS at Week 52.
18. Evaluate the change from both Baselines in lung fibrosis based on high-resolution computed tomography (HRCT) at Week 52.
19. Evaluate the change from both Baselines in diffusing capacity of the lungs for carbon monoxide (DLCO) at Week 52.
20. Evaluate the change from both baselines in serum and plasma biomarkers associated with LPAR1 pathway inflammation and/or fibrosis at [redacted]
21. Evaluate the change from both baselines in [redacted]

4.1.4 Safety and Tolerability Endpoints:

1. Incidence of treatment-emergent adverse events (TEAEs) and AESI
2. Concomitant medication use
3. Change from both Baselines in vital signs
4. Change from both Baselines in 12-lead electrocardiogram (ECG)
5. Change from both Baselines in clinical safety laboratory test results.

4.1.5 Pharmacokinetics (PK) Endpoints:

HZN-825 and metabolite(s) plasma concentrations.

4.2 Study Treatments

The dose regimen for all subjects will be HZN-825 300 mg twice every day for 52 weeks. Subjects will take 2 HZN-825 150 mg tablets orally in the morning and evening with a meal. Subjects will participate in a Safety Follow-up Visit 4 weeks after the last dose of HZN-825.

The treatment group will be based on randomized treatment in previous HZNP-HZN-825-301 trial and denoted as QD/BID (HZN-825 300mg QD/HZN-825 300mg BID), BID/BID (HZN-825 300mg BID/HZN-825 300mg BID), and PLC/BID (Placebo/HZN-825 300mg BID) accordingly.

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4.3 Sample Size and Power Considerations

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

4.4 Interim Analyses

No interim analyses are planned.

5 Study Analysis Sets

Four analysis sets will be defined for this trial.

5.1 Full Analysis Set

The full analysis set (FAS) will include all subjects who were enrolled (i.e., signed the ICF) and who received at least 1 dose or partial dose of HZN-825 in this extension trial. This will be the analysis set used for efficacy data analyses. Subjects will be analyzed according to the treatment group to which they were randomized in the previous trial and combine them as an "Overall" group as appropriate.

5.2 Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least 1 dose or partial dose of HZN-825 in this extension trial. Subjects in this analysis set will be analyzed according to the group determined by the treatment that the subject received in the previous trial and overall, as needed.

5.3 Per Protocol Analysis Set

The Per-Protocol (PP) analysis set will consist of all subjects in the FAS with no major protocol violations that could jeopardize the integrity of data and analysis interpretation. The major protocol violations will be reviewed and approved by Horizon clinician with Biostatistics team. The PP Analysis Set will be used as needed for supportive analysis of the primary endpoint. Subjects in this analysis set will be analyzed according to the treatment group to which they were randomized in the previous trial, and Overall group as needed.

5.4 Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all subjects who received at least 1 dose or partial dose of HZN-825 and had at least 1 PK sample post HZN-825 treatment in this extension trial.

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6 General Considerations

SAS version 9.4 or higher will be used to perform all data analyses.

Summaries of continuous variables will be in terms of the number of observations, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum. Other descriptive statistics (e.g. standard error, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will have the specific descriptive statistics identified with the analysis in the applicable SAP section. All confidence intervals, statistical tests, and P-values will be reported at 2-sided 5% significance level unless otherwise specified.

7 Data Handling

All analyses will be based on observed data. There will be no imputations for missing data except for exploratory purposes as needed.

7.1 Study Day

Study day will be calculated as (date of interest – trial drug start date) + 1 if the date of interest occurs on or after the trial drug start date. If the date of interest occurs before the trial drug start date, then the study day will be calculated as (date of interest – trial drug start date). There will be no study day zero.

There are two types of treatment periods, durations, and time-to-event data.

7.2 Durations and Time to Event Data

Durations are calculated in days as:

- event end date – event start date + 1, if end time or start time not available.
- event end date/time – event start date/time, if both end time and start time available.

Thus, there will be no duration of 0 if end time or start time are not available. If an event has missing or partially missing start or end date, no duration will be calculated.

For elapsed time (e.g. the time to event), use:

- event date/time – reference date/time, (if time available).

Thus, an event which happens on the same date as the reference date will have an elapsed time of 0, if event time or reference time are not available.

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7.3 Baseline Definition

Unless otherwise specified, Baseline is defined as the last non-missing observation prior to the first dose of trial drug at the baseline visit as specified. For observations occurring on the same date as the first dose of trial drug where time is not collected but the protocol specifies the evaluation must occur prior to administration of trial drug, the result occurring on the day of first trial drug administration will be considered as Baseline.

Two types of Baselines are defined as below:

• Trial Baseline, defined as the latest non-missing measurement prior to the first dose of HZN-825 (BID) in this HZNP-HZN-825-302 extension trial.

• HZN-825 Baseline, defined as the latest non-missing measurement prior to the first dose of trial drug (QD, BID, Placebo) in HZN-825-301.

7.4 Visit Window

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

The visit window details will be in the TFL shells document.

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

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

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8 Study Population

8.1 Subject Disposition

The following summaries will be provided by treatment groups that were randomized in previous trial HZNP-HZN-825-301:

Subject disposition presenting the number and percentages of:

- subjects who were eligible for the HZNP-HZN-825-302 trial
- subjects who received trial drug from the HZNP-HZN-825-302 Trial
- subjects who completed the HZNP-HZN-825-302 Trial
- Subjects who prematurely discontinues trial drug and the reasons.

The number of subjects who were eligible for HZNP-HZN-825-302 will be the denominator for calculation of the percentages for the disposition items above. For all other disposition percentages, including the analysis sets below, the number of subjects who received at least one dose of trial drug will be used as the denominator for the calculation.

Number and percentage of subjects in the analysis sets:

- Full Analysis Set (FAS): It consists of all subjects who were enrolled (i.e., signed the informed consent form) and who received at least 1 dose or partial dose of HZN-825 in this extension trial. Subjects will be analyzed according to the treatment group to which they were randomized in the previous trial.
- Safety Analysis Set: It consists of all subjects who receive at least 1 dose or partial dose of HZN-825 in this extension trial. This analysis set will be analyzed according to the group determined by the treatment that the subject received in the previous trial and overall.
- PP Analysis Set: It consists of all subjects in the FAS with no major protocol violations. The PP Analysis Set will be used as needed for supportive analysis of the primary endpoint.
- PK Analysis Set: It includes all subjects who receive at least 1 dose of HZN-825 and have at least 1 PK sample post dose in this study.

Duration (week) of subjects in study will be summarized for subjects in the FAS by treatment group and overall. Duration of subjects in study will be calculated from Day 1 to the end of study date, on which the end of study assessment is performed. For Trial Baseline, treatment periods will start from the first dose day of HZNP-HZN-825-302 to the end of HZNP-HZN-825-302 trial drug day; for HZN-825 Baseline, treatment periods will start from the first dose

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day at trial drug at HZNP-HZN-825-301 to the end of HZNP-HZN-825-302 trial drug day. The number (percent) of subjects with results for each scheduled visit will also be presented.

8.2 Protocol Deviations

Protocol deviations (PDs) occurring after subjects entered the trial are documented during routine monitoring. The PDs are reviewed and categorized as major and minor prior to the database lock. The number and percentage of subjects with major protocol deviations by deviation reason (e.g., nonadherence to trial drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group that received in HZNP-HZN-825-301. A by-subject listing will be provided for all protocol deviations.

8.3 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for the FAS and Safety Analysis Set. These characteristics include age, sex, race, ethnicity, height, weight, body mass index, region, and child-bearing potential (yes, no, not applicable). The use of mycophenolate mofetil (yes/no) and the presence of interstitial lung disease (ILD) (yes/no) based on a Screening HRCT scan will also be summarized, based on the values collected in the clinical database.

Systemic sclerosis history variables will include: time since SSc diagnosis (months), whether the patient has symptoms of SICCA syndrome , time with Raynaud's (months), time since first non-Raynaud's symptoms (months), diffusing capacity of the lungs for carbon monoxide (% predicted), incidence of subjects with gastrointestinal medical history (based on the SOC "gastrointestinal disorders"), incidence of the following symptoms: Raynaud's, digital ulcers, joint contractures, tendon friction rubs, and interstitial fibrosis (HRCT), as well as other related information collected. Systemic sclerosis history will be summarized by treatment group for the FAS.

Demographic data and Baseline characteristics will be provided in subject listings.

8.4 Prior and Concomitant Medications

Prior and concomitant medications information will be collected in the database. Prior and concomitant medication verbatim terms in the eCRFs will be mapped to Anatomical Therapeutic Chemical (ATC) level 4 and preferred terms using the WHO Drug Global B3 Mar2021. Prior and concomitant medications will be summarized by presenting the counts and percentage of subjects using medications overall and by each treatment group based on Safety Analysis Set. Summaries will be provided by ATC Level 4 term and PT. Medication summaries will be sorted alphabetically by ATC Level 4 and by PT within ATC Level 4. Subjects will be counted only once for each medication class and each preferred drug name.

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Prior and concomitant medications will be listed together with a designation to identify the medications as prior and/or concomitant and sorted by start date.

8.4.1 Prior Medications

Prior medications will be presented separately from concomitant medications in a summary table. Any medication with a stop date prior to the date of the first dose of the study will be considered a prior medication.

8.4.2 Concomitant Medications

Any medication that is ongoing, has a start date on or after the first dose of study, or a stop date on or after the first dose date will be considered a concomitant medication. If stop date is missing, the medication is considered as ongoing.

Prior and concomitant medications will be summarized for treatment groups of the previous trial and overall by ATC level 4 term and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class and preferred name but will only be counted once in the summary.

Prior and concomitant medications and concomitant procedures will be listed for all subjects.

9 Efficacy Analyses

All efficacy analyses will be analyzed based on FAS. The PP Analysis Set will be used as needed for supportive analysis of the primary endpoint. There are two types of Baselines (Trial Baseline and HZN-825 Baseline) used in analyses as appropriate. Because this is an open-label, single-arm trial, no formal statistical analyses will be conducted. The comparisons between the treatment groups and p-values are for descriptive purpose.

9.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint will be the change from both Baselines (Trail Baseline and HZN-825 Baseline) in FVC% predicted at Week 52.

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

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analysis; if the model does not converge, other covariance matrices or descriptive statistics will be considered. The least squares mean (LS mean) difference in change from Trial Baseline to Week 52 in 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. A similar process for the FVC % predicted for the change from HZN-825 Baseline will also be performed.

9.2 Exploratory Efficacy Endpoint Analyses

Analysis of the exploratory efficacy endpoints will be conducted in the order they are listed below for both changes from HZN-825 Baseline and Trial Baseline to Week 52 as needed.

The analysis will follow the primary analysis of the primary efficacy endpoint. The analysis will be based only on observed data.

Exploratory endpoints will be summarized at each time point. Change from HZN-825 Baseline and Trial Baseline will be evaluated separately.

9.2.1 Change from both Baselines in HAQ-DI at Week 52

The key exploratory efficacy endpoint is the change from both baselines in HAQ-DI.

The HAQ-DI 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 involved 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 form another person is needed are also assessed.

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

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

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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

The HAQ-DI value itself is derived from a combination of the scores of the 8 categories of function and use of devices to result in one disability index, which ranges from 0 to 3 [Bruce B, Fries JF et al, 2003]. The HAQ-DI is calculated by scoring the answer to each question in the HAQ from 0 to 3, with 0 representing the ability to do without any difficulty, and 3 representing inability to do. Any activity that requires assistance from another individual or requires the use of an assistive device raises a 0 or 1 score to a 2. The highest score for each of the 8 domains is summed (range from 0 to 24) and divided by 8 to yield, on a scale with 25 possible values, a Functional Disability Index with a range from 0 to 3.

If a domain has all responses missing (including aids/devices) then the domain is considered missing. If some of the questions have a result and/or the aids/devices is checked, then use available values to calculate a domain score. The disability index is based on the number of domains answered and is computed only if the subject completes answers to at least 6 domains. That is, if 6 domains are non-missing, then the average of the 6 available scores will determine the Functional Disability Index. If < 6 domains are non-missing, then the HAQ-DI score will be missing.

If "Other" option is checked in either of the "AIDS AND DEVICES" sections of the questionnaire, the corresponding "Other, Specify" field will be reviewed and categorized by Horizon Therapeutics into an appropriate domain of function, so it can be incorporated into the score.

Analysis will follow that of the primary analysis of the primary efficacy endpoint, except that the analysis will be based only on observed data.

9.2.2 Change from both Baselines in MDGA at Week 52

The Physician Global Assessment (MDGA) is an 11-point 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.

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The MDGA will be tested in the same manner as that described for the primary analysis of the primary endpoint, but based only on observed data.

9.2.3 Change from both Baselines in PTGA at Week 52

The Patient Global Assessment (PTGA) is an 11-point scale ranging from 0 to 10 (0=excellent to 10=extremely poor) on which the patient rates their overall health over the past week.

The PTGA will be tested in the same manner as that described for the primary analysis of the primary endpoint, but based only on observed data.

9.2.4 Change from both Baselines in the Physical Effects subscale of the SSPRO-18 at Week 52.

The SSPRO-18 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. Recall is the past 4 weeks. Response options are on a 0-6 point scale where 0 is 'not at all' and 6 is 'very much.' The physical effects or symptoms domain includes 5 items, physical limitations has 4 items, emotional effects includes 6 items and social effects has 3 items. A total score and domain specific scores (physical effects, physical limitations, emotional effects, and social effects) can be calculated and transformed to a 0 – 100 scale, with higher scores indicating more severe impact of skin problems on the patient's quality of life. The SSPRO-18 Physical Effects subscale will be tested in the same manner as that described for the primary analysis of the primary endpoint, but based only on observed data.

Missing items will be imputed according to the instructions for the questionnaire. If the scoring manual for the SSPRO-18 does not indicate how to impute missing data, then the subscale with missing items will be considered missing.

9.2.5 Change from both Baseline in the Physical Limitations subscale of the SSPRO-18 at Week 52.

The SSPRO-18 Physical Limitations subscale will be tested in the same manner as that described for the primary analysis of the primary endpoint, but based only on observed data.

Missing items will be handled as indicated in Section 9.2.4

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9.2.6 Proportion of subjects with an mRSS decrease of ≥5 points and 25% from both Baselines at Week 52.

The mRSS is a validated method for estimating skin thickening [Khanna et al, 2017]. Seventeen different body areas are scored as normal (0), mild thickening (1), moderate thickening (2) and severe thickening (3). The scores selected for each body area are summed for a total score, which has a maximum score of 51.

Missing body area scores will be imputed according to the scoring instructions for this tool. If the scoring manual for the mRSS does not indicate how to impute missing data, then the body area with missing items and corresponding total score will be considered missing.

The proportion of subjects with an mRSS decrease in ≥ 5 points and 25% from both baselines at Week 52 will be analyzed with observed data using a stratified logistic regression model. Baseline value and treatment will be considered as factors in the model and use of mycophenolate mofetil [yes/no] and presence of ILD [yes/no]) will be considered as stratification factors. The probabilities of risk differences between each dose and reference group with its 95% confidence intervals will be presented. Subjects missing mRSS scores at Week 52 will be imputed as non-responders.

9.2.7 Responder rate (defined as ACR-CRISS [predicted probability] of at least 0.6) at Week 52

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 physician 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.

- 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

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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, high resolution computed tomography to confirm ILD (if previous scan did not show ILD) and FVC % predicted <80% predicted;
- New onset of left ventricular failure (defined as ejection fraction ≤45%) requiring treatment;
- New onset of pulmonary hypertension (PAH) on right heart catheterization requiring treatment.
- Gastrointestinal dysmotility requiring enteral (tube feeding) or parenteral nutrition

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- 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 MDGA [Khanna et al, 2016].

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 MDGA, and $\Delta_{HAQ\text{-}DI}$ is the change in HAQ-DI. All changes are absolute change ($Time_2 - Time_{baseline}$). Subjects missing one or more components of the equation will be classified as non-responders. The MDGA and PTGA are the 11 point scales rating the subject's overall health during the preceding week by physician and patient, respectively.

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 responder rate by ACR-CRISS at Week 52 will be analyzed with a stratified logistic regression model. Both baselines value and treatment will be considered as factors in the model and use of mycophenolate mofetil [yes/no] and presence of ILD [yes/no]) will be considered as stratification factors. The probabilities of risk differences between each dose and placebo with its 95% confidence intervals will be presented.

9.2.8 Proportion of subjects with an improvement in ≥3 of 5 core measures from both Baseline at Week 52

The proportion of subjects with an improvement in ≥3 of 5 core measures from both Baselines: ≥20% in mRSS, ≥20% in HAQ DI, ≥20% in PTGA, ≥20% in MDGA and ≥5% for FVC % predicted at Week 52 (ACR-CRISS-20) will be analyzed with the same model described in Section 9.2.7. The ACR-CRISS-20 is defined as ≥3 core measures of ≥20% in mRSS, ≥20% in HAQ DI, ≥20% in PTGA, ≥20% in MDGA and ≥5% for FVC % predicted.

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9.2.9 Change from both Baseline in the SSPRO-18 at Week 52.

The SSPRO-18 scale and change from baseline in each of the domains and the total score of the SSPRO-18 scale will be summarized for each time-point by treatment group. Comparisons of each dose of HZN-825 at Week 52 will be tested in the same manner as that described for the primary analysis of the primary endpoint, but based only on observed data.

Missing items will be handled as indicated in Section 9.2.4

9.2.10 Change from both Baseline in each scale of the UCLA SCTC GIT 2.0 and the total GIT score at Week 52.

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

The UCLA SCTC GIT 2.0 has 7 scales—reflux, distension/bloating, fecal soilage, diarrhea, social functioning, emotional well-being, and constipation; a total GIT score is also calculated to capture overall burden of SSc-associated gastrointestinal involvement. Items are scored on a 0 (no days) to 3 (5 – 7 days) scale (except questions 15 and 31 are yes/no questions, and are scored as 1/0, respectively) and do not require conversion to a 0 to 100 scale. The scores of the items composing each scale are summed and then divided by the total number of items in scale. For reflux, total item score will be divided by 8. For distension/bloating, total item score will be divided by 4. For fecal soilage, total item score will be divided by 3. For diarrhea, total item score will be divided by 2. For social functioning, total item score will be divided by 6. For emotional well-being, total item score will be divided by 9. For constipation, total item score will be divided by 4.

Missing items for UCLA SCTC GIT 2.0 scales and total score will be imputed according to the instructions for the questionnaire. If the scoring manual does not indicate how to impute missing data, then the scale with missing items and total score will be considered missing.

Each scale of the GIT and total GIT score with corresponding change from baseline will be summarized descriptively at each time-point by treatment group. Corresponding change from Week 52 summaries will also be provided. Comparisons of each dose of HZN-825 at Weeks

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52 for the change from both baselines will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 9.1, but based only on observed data.

9.2.11 Change from both Baseline in Raynaud's phenomenon using the Raynaud's Assessment at Week 52.

The Raynaud's Condition Score Diary captures frequency, duration and severity of Raynaud's phenomenon activity and has face, content, criterion, discriminant and construct validity in subjects with SSc [Merkel et al., 2003]. Subjects will be provided an electronic device to capture symptoms daily through Week 52. The Raynaud's Assessment score includes a 11-point scale ranging from 0 to 10 (0=no difficulty to 10=extreme difficulty) on which the patient rates the difficulty they had with their Raynaud's condition, the count of the Raynaud's attacks that were experienced that day, and the number of minutes the longest attack lasted.

Since this is a daily diary, for each of the 3 components of the Raynauds Assessment, an analysis value will be calculated for Week 52. The analysis value will be the average of the results collected within the 30 days prior to the attended (or mapped/windowed) study day corresponding to Week 52. The resulting analysis values will be summarized descriptively by visit week and treatment group. Baseline values will be summarized descriptively by treatment group as well. Comparisons of each dose of HZN-825 at Week 52 for the change from baseline will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 9.1, but based only on observed data.

9.2.12 Change from both Baselines in the SHAQ at Week 52.

The SHAQ consists of the HAQ-DI (8 domains) and also includes a visual assessment scale (VAS) for pain and the following scleroderma-specific VASs: patient global assessment, vascular, digital ulcers, lung involvement and gastrointestinal involvement [Steen and Medsger, 1997]. The 5 scleroderma-specific VASs ask subjects how much symptoms interfere with daily activities. A visual analog scale (VAS) of 0-100 is used for each item with a one-week recall period, except for the overall global item which asks the participant to rate their condition "today". Each item is considered separately and reported individually. A composite VAS score is not created nor are the individual VAS scores incorporated into the HAQ-DI score.

Each SHAQ score with corresponding change from baseline will be summarized descriptively at each time-point by treatment group. Comparisons of each dose of HZN-825 at Week 52 for the change from baseline will be done for each VAS score and will be tested

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in the same manner as that described for the primary analysis of the primary endpoint in Section 9.1, but based only on observed data.

9.2.13 Change from both Baseline in SScQoL scores at Week 52.

The SscQoL is a validated tool that has 29 questions divided into 5 subscales relating to physical functioning (score range: 0 to 6), emotional functioning (0 to 13), social functioning (0 to 6), sleep (0 to 2) and pain (0 to 2), which are important disease-specific factors associated with quality of life in SSc [Sierakowska et al., 2019]. The score for each subscale is determined by summing the 'true' responses for the questions corresponding to the subscale, where each 'true' response has a score of 1. Total score is calculated accordingly. High scores indicate a greater impact of the disease.

If any question is missing, then the corresponding subscale and the total score will be missing.

Each SscQoL subscale with corresponding change from both baselines to Week 52 will be summarized descriptively at each time-point by treatment group. Comparisons of each dose of HZN-825 at Week 52 for the change from baseline to Week 52 in each subscale will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 9.1, but based only on observed data.

9.2.14 Change from both Baselines in SF-12 scores at Week 52.

The SF-12 [Ware, et al., 1996] is a 12-item survey used to assess general health-related quality of life. The SF-12 items are scored to generate a physical component score (PCS) and mental component score (MCS) from the subject's perspective [Ware, et al, 1998]. The SF-12 examines 8 domains of health outcomes, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health.

Missing items and corresponding calculation of domain, PCS, and MCS scores will be handled according to the scoring instructions for the questionnaire.

Each domain of the SF-12, the PCS, and the MCS scores with corresponding change from both baselines will be summarized descriptively at each time-point by treatment group. Corresponding change from Week 52 summaries will also be provided. Comparisons of each dose of HZN-825 at Week 52 for the change from both baselines to Week 52 will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 9.1, but based only on observed data.

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9.2.15 Change from both Baseline in pain and pain component scale scores at Week 52.

Subjects complete a pain questionnaire that has 3 questions regarding the severity of pain experienced during the past week due to Raynaud's, arthritis and finger ulceration and/or calcinosis. Subjects rate their pain on an 11-point scale from 0 (no pain) to 10 (the worst pain imaginable).

Missing values will not be imputed.

Each pain score and change from baseline in the pain score will be summarized for each time-point by treatment group. Comparisons of each dose of HZN-825 at Week 52 will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 9.1, but based only on observed data.

9.2.16 Change from both Baseline in the FACIT-F score at Week 52.

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

Each response to the 13 items is transposed according to a reversal algorithm on the scoring sheet, the sum of the transposed items is taken and multiplied by 13. The multiplied value is then divided by the number of questions answered. This results in a fatigue subscale score ranging from 0 to 52. The higher the score, the better the quality of life (lower fatigue).

Missing items for FACIT-F score will be handled according to the instructions for the questionnaire for the calculation of the Fatigue Subscale Score.

The FACIT-F subscore and change from baseline in the FACIT-F subscore will be summarized for each time-point by treatment group. Comparisons of each dose of HZN-825 at Week 52 will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 9.1, but based only on observed data.

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9.2.17 Change from both Baselines in the mRSS at Week 52.

The mRSS total score will be derived using the method described in Section 9.2.6. Comparisons of each dose of HZN-825 at Week 52 will be tested in the same manner as that described for the primary analysis of the primary endpoint in Section 9.1, but based only on observed data.

9.2.18 Other efficacy endpoints change from Baselines at Week 52.

Descriptive statistics will be used for other efficacy endpoints from both Baselines at Week 52 including lung fibrosis in subjects with suitable Baseline high-resolution computed tomography (HRCT), diffusing capacity of the lungs for carbon monoxide (DLCO), serum and plasma biomarkers associated with LPAR1 pathway, inflammation and/or fibrosis, and [redacted]

10 Safety and Tolerability Analyses

All safety analyses will be based on the Safety Analysis Set. All safety endpoints will be summarized using descriptive statistics for both Baselines.

10.1 Extent of Exposure

Exposure to HZN-825 in HZN-825-302HZNP-HZN-825-302 will be descriptively summarized by treatment group: drug exposure, measured as duration of treatment (days treated), is the number of days on treatment based on the first and last days of treatment with the study medication (last day of study medication – first day of study medication + 1). This will be based on the trial drug dispensation CRF page.

Summary statistics will be provided for the duration of exposure to study medication (days) by treatment group. Additionally, a categorical breakdown of duration of treatment will be provided, including the following categories: 0 – 3 months, > 3 to 6 months, > 6 to 9 months, and > 9 to 12 months, > 12 to 15 months, > 15 to 18 months, > 18 to 21 months, > 21 to 24 months.

Summary statistics will also be presented for the total number of HZN-825 doses and total dose administered by treatment group.

10.2 Treatment Compliance

The calculation of overall compliance is based on all doses in HZNP-HZN-825-302.

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The formula for compliance (%) is calculated as: (cumulative actual dose / prescribed dose for time spent on study treatment)*100.

The prescribed dose for time spent on study treatment is calculated as: (date of last administration – date of first administration + 1) * daily prescribed dose.

The following summaries will be provided by treatment group:

- Summary statistics for percentage overall compliance.
- Percentage overall compliance categorized by frequencies < 70%, 70%-80%, 80%-90%, and > 90%.

A subject individual treatment compliance listing will be provided.

10.3 Adverse Events

10.3.1 Treatment-Emergent Adverse Events.

Treatment-emergent adverse events (TEAEs) are defined as any AEs with an onset date on or after the trial drug start date and time (if known) and no later than 28 days after permanent discontinuation of trial drug.

Refer to the table, listing, and figure shell document for determination of TEAE status in adverse events that are missing critical AE date start and stop information. All TEAEs will be evaluated for both treatment periods (start from first dose at HZNP-HZN-825-301 and HZNP-HZN-825-302 to the end of HZNP-HZN-825-302). Imputed dates are only used for classification of TEAEs.

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

Follow-up AEs are defined as any AE occurring > 28 days after permanent discontinuation of trial drug for subjects who prematurely discontinue the study medication prior to 52 weeks (i.e. 392 days after first trial drug intake). Follow-up AEs will be identified in the listings as such. Related SAEs will be followed up until resolved or until the event stabilizes and the overall clinical outcome has been ascertained.

The Verbatim terms in the eCRFs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using the current version of MedDRA. Adverse events will be graded for

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severity using the Rheumatology Common Toxicity Criteria (RCTC) v2.0 [Woodworth et al., 2007].

For summaries by SOC, PT, and maximum severity, a subject will only be counted once for each SOC based on the maximum severity level reported for that SOC and once for each unique PT within that SOC level at the maximum intensity level reported for that PT.

For summaries by SOC and PT only, a subject will be counted at most once at the SOC level and at most once at each unique PT within the SOC level. Summaries presenting the frequency of TEAEs by SOC and PT will be ordered alphabetically by SOC and then, within a SOC, alphabetically by PT.

Event Adjusted Incidence Rate (EAIR) is defined as number of subjects with events / total subject-years. Subject-years for each subject will be calculated as (date of first event occurred – first dose date +1)/365.25. For subjects without an event, subject-years for each subject = (last day in study – first dose date +1)/365.25.
EAIR will be summarized by SOC and PT as needed for TEAE.

Events for which the investigator did not record relationship to trial drug will be considered related to trial drug for summary purposes. However, by-subject data listings will show the relationship as missing. No imputation will be done in case of missing study treatment relationship for non-treatment emergent AEs.

The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

Summaries of the following types will be presented:

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group.

The following AEs summaries will be provided by SOC, PT, and treatment group. AE summaries followed by an asterisk(*) will include the number of events and the corresponding incidence of events per PYE.:

- All TEAEs by maximum severity
- All treatment-emergent SAEs*
- All treatment-related TEAEs*
- All treatment-related TEAEs by maximum severity
- All treatment-related treatment-emergent SAEs
- All TEAEs meeting CRISS criteria
- All TEAEs leading to permanent withdrawal of any trial drug
- All TEAEs leading to death (ie, outcome of death)
- All follow-up adverse events
- All serious follow-up adverse events
- Subject incidence of AESIs: [redacted]

A brief, high-level summary of AEs described above will be provided by treatment group for the study treatment period and by the number and percentage of subjects who experienced the above AEs. All deaths observed in the trial will also be included in this summary. For the overall summary, the category of "TEAEs by maximum severity" described above will be replaced by AEs with severity > Grade 3.

The frequency of TEAEs occurring in > 5% of subjects in any treatment group will be summarized by treatment, primary SOC, and preferred term. A similar summary will be created for serious TEAEs occurring in > 3% of subjects in any treatment group by primary SOC and preferred term.

An adverse event plot will be created with AE incidences and risk differences (with corresponding exact 95% confidence interval) plotted together for the adverse events occurring in >5% of subjects in any treatment group. A similar plot will be created for SAEs occurring in > 3% of subjects in any treatment group.

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

- All AEs, indicating whether the event is treatment-emergent
- SAEs

- Deaths
- AEs leading to permanent withdrawal of trial drug
- Adverse events of special interest: [redacted]

10.3.2 Adverse Events of Special Interest

[redacted] is considered an adverse event of specifical interest (AESI) in this trial. The AESI is collected from adverse event report and from [redacted] procedure.

[redacted]

[redacted] procedure data will be evaluated for both treatment periods (start from first dose at HZNP-HZN-825-301 and at HZNP-HZN-825-302 to the end ofHZNP-HZN-825-302).

Symptoms reported on the [redacted] procedure may not be reported as adverse events, and will not be reconciled as such. Any spontaneously reported signs or symptoms possibly associated with [redacted] will be captured as AEs. These will be identified based on the flag within the dataset and/or programmatically using the standard MedDRA query (SMQ) search criteria as needed.

10.3.3 Clinical Laboratory Evaluations

10.3.3.1 Summaries of Laboratory Results

Laboratory data collected during the trial will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set. Laboratory parameters to be summarized are listed in Table 5.

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Table 5 Lab Parameters

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

Laboratory results collected in conventional units will be converted to International System of Units (SI) for all summaries and listings. Clinical laboratory test results (Hematology, Chemistry, Lipids and Coagulation, and Urinalysis) and their changes from baseline will be summarized by visit and treatment group using descriptive statistics.

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

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

For urinalysis tests, results will be classified as normal or abnormal. Results out of range will be identified as such on subject listings. Shift tables for urinalysis results using categories of normal and abnormal, comparing laboratory test results from Baseline to each visit will be presented with percentages based on subjects with a non-missing value at Baseline and post-baseline visit.

A listing of urine pregnancy test results will be produced.

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

No formal statistical testing is planned.

Shift plots may be produced for selected laboratory values.

Laboratory results will be evaluated from Trail and HZN-825 Baselines to the end of HZNP-HZN-825-302 separately as needed.

10.3.3.2 Summaries Liver Function Tests

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

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

- Alanine aminotransferase (ALT):
  (a) > 3 x ULN;
  (b) > 5 x ULN
  (d) > 8 x ULN;
  (e) >20 x ULN
- AST or ALT:
  (a) > 3 x ULN;

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(b) > 5 x ULN
- Total bilirubin:
  (a) > 1.5 x ULN;
  (b) > 2 x ULN
  (c) > 3 x ULN
- Alkaline phosphatase (ALP):
  (a) > 1.5 x ULN;
  (b) > 2 x ULN
  (c) > 3 x ULN
- Gamma Glutamyl Transferase (GGT):
  (a) > 2.5 x ULN;
  (b) > 5 x ULN
  (c) > 20 x ULN

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

The summary will include data from all postbaseline visits up to 28 days after the last dose of trial drug.

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

A listing of subjects who met at least 1 of the above criteria will be provided.

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

Liver function data will be evaluated from Trail and HZN-825 Baselines to the end of HZNP-HZN-825-302 separately as needed.

10.3.4 Vital Sign

Vital signs (blood pressure, heart rate, respiratory rate, temperature) will be measured at all clinic visits.

Descriptive summaries of observed and change from baseline values will be presented for each vital sign parameter and weight by treatment group and visit. A shift table for vital signs by RCTC grade and visit will be summarized.

In the case of multiple values in an analysis window, data will be selected for analysis as described in the TLF shells document. No formal statistical testing is planned.

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A by-subject listing of vital signs and weight will be provided by subject ID number and time point in chronological order. High or low values will be flagged.

All data will be evaluated from Trail and HZN-825 Baselines to the end of HZNP-HZN-825-302 separately as needed.

10.3.5 Electrocardiogram Results

12-lead Electrocardiogram (ECG) will be performed at Screening (Baseline) and Weeks 1, 4, 16, 28, and 52. The results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated as clinically significant (CS) or not clinically significant (NCS) by the investigator.

Descriptive summaries of observed and change from both baselines values will be presented for each ECG parameter by treatment group and visit, including HR, PR, QRS, QT, and QTcF. ECG shift tables will be presented providing the count of subjects with each type of finding (normal, abnormal – NCS, or abnormal – CS) at both baselines compared to each post-baseline visit by treatment group with percentages based on subjects in the Safety Analysis Set with a non-missing value at the baseline and post-baseline visit.

Further, a summary will be provided for the count and percentage by classified categories. The abnormal post-dose QTcF interval values obtained during the trial will be summarized within the following categories:

- > 450 msec
- > 480 msec
- > 500 msec
- QTcF increase from Baseline > 30 msec
- QTcF increase from Baseline > 60 msec

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

All ECG data will be evaluated from Trail and HZN-825 Baselines to the end of HZNP-HZN-825-302 separately as needed.

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11 Pharmacokinetic Analyses

PK data will be analyzed using the PK Analysis Set. Plasma concentrations of HZN-825 and metabolite(s) (if applicable) in HZNP-HZN-825-302 will be summarized descriptively, including arithmetic means, standard deviations, geometric means, coefficients of variation, medians, first and third quartiles and ranges, by actual treatment and by time point. A listing including subject, week/time point (actual, planned), treatment and plasma concentrations.

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

Population PK analysis and exposure-response analysis may be performed, with details reported separately.

12 Autoantibody Analyses

The presence and levels of anticentromere antibody, anti-RNA polymerase antibody, anti-topoisomerase 1 and anti-U1 small nuclear ribonucleoprotein will be evaluated and summarized descriptively for the Safety Analysis Set.

A listing of all autoantibody results will be produced.

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14 Appendix, Schedule of Assessments (Clinical Study Protocol v2.2)

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

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	Open-label Treatment Period (HZN-825 300 mg BID)										Safety Follow-up Visit [1]
Trial Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 4 weeks after last dose of HZN-825**
Trial Week (W)	**Day 1 [2]**	**W4**	**W10 [1]**	**W16**	**W22 [1]**	**W28**	**W34 [1]**	**W40**	**W46 [1]**	**W52/PD [4]**	
Visit Window (±days)		**(±3)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±14)**
SScQoL	X [3]					X				X	
SF-12	X [3]					X				X	
Pain questionnaire	X [3]					X				X	
Fatigue (FACIT-F)	X [3]					X				X	
Raynaud's assessment [7]	X [3]				X				X		
Anchor questions											
ACR-CRISS (last week)	X [3]			X		X		X		X	
ACR-CRISS (overall health and change since start of trial)						X				X	
FVC (last week)	X [3]			X		X		X		X	
FVC (change since start of trial)						X				X	
HAQ-DI (last week)	X [3]			X		X		X		X	
HAQ-DI (change since start of trial)						X				X	
SSPRO-18 (last week)	X [3]					X		X		X	
SSPRO-18 (change since start of trial)						X				X	

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	Open-label Treatment Period (HZN-825 300 mg BID)										Safety Follow-up Visit [1]
Trial Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 4 weeks after last dose of HZN-825**
Trial Week (W)	**Day 1 [2]**	**W4**	**W10 [1]**	**W16**	**W22 [1]**	**W28**	**W34 [1]**	**W40**	**W46 [1]**	**W52/PD [4]**	
Visit Window (±days)		**(±3)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±14)**
Pregnancy test [8]	[redacted]										
Physical examination [9]	X [3]					X				X	X
Vital signs [10]	X [3]	X	X	X	X	X	X	X	X	X	X
[redacted]											
12-lead electrocardiogram [11]	X [3]	X		X		X				X	
Echocardiogram [11]	X										
Clinical laboratory safety tests [12]											
Chemistry	X [3]	X	X	X	X	X		X		X	X
Lipids	X [3]					X				X	
Hematology	X [3]	X	X	X	X	X		X		X	X
Urinalysis	X [3]	X	X	X	X	X		X		X	X
ESR[13] and hsCRP	X [3]									X	X
Autoantibodies [14]	X [3]									X	
PK samples [15]	X [3]	X		X		X		X			
Serum Biomarkers[16]	[redacted]										
Plasma Biomarkers[16]											
Adverse event assessment [17]	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications [18]	X [3]	X	X	X	X	X	X	X	X	X	X

ACR-CRISS=American College of Rheumatology-Composite Response Index in Systemic Sclerosis; BID=twice daily; DLCO=diffusing capacity of the lungs for carbon monoxide; ESR=erythrocyte sedimentation rate; FACIT-F=Functional Assessment of Chronic Illness Therapy – Fatigue Scale FVC=forced vital capacity; HAQ-DI=Health Assessment Questionnaire – Disability Index; HRCT=high resolution computed tomography; hsCRP=high-sensitivity C-reactive

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protein; MDGA=Physician Global Assessment; 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; SF-12=SF-12® Health Survey; SHAQ=Scleroderma Health Assessment Questionnaire; SLCO=solute carrier organic anion transporter family member; SSc=systemic sclerosis; SScQoL=Systemic Sclerosis Quality of Life Questionnaire; UCLA SCTC GIT 2.0=University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract; SSPRO=scleroderma skin patient-reported outcome; VAS=visual analog scale; W=Week; WOCBP=women of childbearing potential

1. Visits may be conducted as home health visits, as available within local regions.
2. On Day 1 (Baseline), subjects will receive the first dose of HZN-825 in this extension trial in the clinic. All Day 1 assessments should be performed before the first dose of trial drug is administered in the clinic.
3. Performed as part of the Week 52 Visit of HZNP-HZN-825-301; if applicable, the result will be considered a Trial Baseline value for this extension trial.
4. Except when strictly unavoidable, the same person should perform the assessment at each evaluation during the trial. The mRSS assessment should be performed by a qualified Investigator (or designee).
5. The lung HRCT scan should be performed within ±2 weeks of the Week 52/PD Visit.
6. DLCO can be assessed within ±2-weeks of the Week 28 and Week 52/PD Visits.
7. Daily electronic diaries will be completed for 4 weeks starting on Day 1, 4 weeks starting at the Week 22 Visit and 4 weeks starting at the Week 46 Visit.
8. Perform for WOCBP. Serum pregnancy test at [redacted] (or as needed). Urine pregnancy tests should also be done every 4 weeks after Day 1, which includes both in-clinic testing at scheduled visits prior to dosing [redacted] and at home (also a ±7-day window) by the subject and reported to the site [redacted] A urine pregnancy test will also be done at the Safety Follow-up Visit.
9. A complete physical examination, including but not limited to cardiac, pulmonary, neurologic and skin assessments, as well as directed rheumatology assessments [redacted]
10. Vital signs (blood pressure, heart rate, respiratory rate, temperature) will be measured at each visit.
11. Additional electrocardiograms or echocardiograms will be conducted, if clinically indicated. A standard transthoracic echocardiogram will be conducted on Day 1. However, an echocardiogram that has been performed during HZNP-HZN-825-301 and within the 3 months prior to HZNP-HZN-825-302 Day 1 can serve as the Trial Baseline echocardiogram if the subject has been clinically stable.
12. See Section 9.5.3.8 for details.
13. ESR must be processed within 1 hour of the blood draw.
14. Autoantibodies include anti-centromere antibody, anti-RNA polymerase antibody, anti-topoisomerase 1 and anti-U1 small nuclear ribonucleoprotein.
15. PK samples will be collected at each of the following visits: Day 1 (pre-dose), Week 4 (pre-dose and 2 to 4 hours post-dose) and Weeks 16, 28 and 40 (pre-dose). Note: all pre-dose samples will be collected prior to any HZN-825 administration for the day.
16. Blood samples will be collected for serum and plasma biomarkers prior to dosing on [redacted] as well as at the [redacted] Visit.
17. Adverse events occurring or worsening after the first dose of HZN-825 on Day 1 through the Safety Follow-up Visit will be considered treatment-emergent adverse events for this trial. All adverse events that occur from the signing of informed consent through the Safety Follow-up Visit will be recorded. The subject should be assessed for the development of new onset of scleroderma renal crisis, new onset of left ventricular failure, new onset of pulmonary arterial

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hypertension or right heart catheterization requiring treatment, gastrointestinal dysmotility requiring enteral (tube feeding) or parenteral nutrition or digital ischemia with gangrene, amputation or hospitalization requiring treatment.

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

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15 Approvals Form

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

[redacted], PhD Director, Biostatistics Name, Title	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 3/15/2024 | 4:26:45 PM GMT [redacted] Signature/Date
[redacted], MD Medical Director Name, Title	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 3/18/2024 | 11:53:05 PM GMT [redacted] Signature/Date

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