Janssen Pharmaceutical K.K.*

Clinical Protocol

Protocol Title
A Multicenter, Randomized, Placebo-controlled, Double-blind, Proof-of-concept Study of Guselkumab in Participants with Systemic Sclerosis

Protocol CNTO1959SSC2001; Phase 2a
AMENDMENT 5

CNTO1959 (guselkumab)

* This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

Status: Approved
Date: 15 November 2022
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-RIM-152487, 7.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	15 November 2022
Amendment 4	25 August 2022
Amendment 3	30 September 2021
Amendment 2	20 May 2021
Amendment 1	25 March 2021
Original Protocol	20 October 2020

Amendment 5 (15 November 2022)

Overall Rationale for the Amendment: To Abolish Week 24 DBL and Internal Decision Committee (IDC).

The changes made to the clinical protocol CNTO1959SSC2001 as part of Protocol Amendment 5 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis OVERALL DESIGN 4.1 Overall Design	The following text was modified: Two~~Three~~ planned database locks (DBLs) will occur: ~~when all participants complete the Week 24 visit (hereinafter referred to as "Week 24 DBL")~~, EOS of the main study (Week 52 visit for participants who entered LTE or ~~Week 60~~ safety follow up visit for participants who did not enter LTE, hereinafter referred to as "Week 52 DBL"), and EOS of LTE (Week 112 visit, hereinafter referred to as "Final DBL"). ~~Of note: if the LTE is terminated as per the IDC's (Internal Decision Committee) recommendation (Section 9.5), there will be 2 DBLs (Week 24 and Week 52 DBLs) only and the LTE data collected for the participants who already entered LTE at the time of Week 24 DBL will be analyzed at Week 52 DBL, along with the data through Week 52 or 60 visit.~~	To Abolish Week 24 DBL and IDC in order to avoid unblinding for part of the sponsor personnel during double-blind period (until Week 52) from data integrity perspective.
1.2 Schema Figure 1	Week 24 DBL was deleted.	
4.1.1 Long-term Extension	The following text was deleted: ~~An internal decision committee (IDC) will be established to determine whether the LTE can continue or not based on the data from Week 24 DBL, as a risk mitigation if few benefits of guselkumab has been observed (Section 9.5). The decision will be informed to investigators by sponsor's study site monitor, only if LTE is terminated. Investigators must inform all participants to take the following actions;~~ • ~~Participants who have already entered LTE will discontinue study intervention, and perform Early termination visit and safety follow up visit~~	

Section Number and Name	Description of Change	Brief Rationale
	~~(Week 112) as per Section 1.3.~~ • ~~Participants who are still in the main study will continue study intervention until Week 52, and follow-up visit (Week 60) to complete the study as per Section 1.3, unless there is any safety concern.~~ • ~~If the termination decision is made for safety concern, then all participants will be discontinued from both LTE and main study.~~	
6.3 Measure to Minimize Bias: Randomization and Blinding Blinding	The following text was modified: ~~Under normal circumstances, the blind should not be broken until the Week 52 DBL. However, selected sponsor personnel will be unblinded for analysis after the Week 24 DBL has occurred.~~ All sponsor personnel, site personnel and participants will remain blinded to the treatment assignments until the Week 52 DBL. ~~An unblinding plan will be developed and finalized prior to any unblinding to designate sponsor personnel who will have access to the unblinded data during the period from the Week 24 DBL to the Week 52 DBL.~~ ~~An internal decision committee (IDC) will be established to determine whether the LTE can continue or not with the data from Week 24 DBL and the IDC member will be unblinded to all Week 24 data to facilitate the decision making (Section 9.5).~~	
9.4.1 General Considerations	The following text was modified: ~~The primary~~ An interim analysis will be performed when all participants have completed the Week 52 ~~24~~visit or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit or discontinued earlier. ~~Other analysis timepoints are described in Section 9.4.6.~~	
9.4.6 Other Analyses Interim Analyses	The following text was modified: ~~The primary analysis will be performed when all participants have completed Week 24 or discontinued earlier. Internal Decision Committee (IDC) will determine whether the LTE can continue or not based on the primary analysis results. In addition, selected sponsor personnel will be unblinded at the primary analysis for internal decision making. Details of the unblinding will be specified in SAP.~~ ~~If LTE continues, a~~An interim analysis will be performed when all participants have completed EOS of the main study ~~Week 52 or discontinued earlier.~~ All sponsor personnel will be unblinded at the analyses for internal decision-making and/or interactions with health authorities.	
9.5 Internal Decision Committee	Section deleted.	

Section Number and Name	Description of Change	Brief Rationale
6.8 Concomitant Therapy NSAIDs or Other Analgesics	The following text was modified: For participants who receive corticosteroids and/or NSAIDs, prophylactic treatment ~~with~~ such as rebamipide, ~~proton pump inhibitors~~ or H2-receptor blockers should be considered. Prophylactic treatment should be added according to the investigator's discretion.	Change to appropriate prophylaxis.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Multicenter, Randomized, Placebo-controlled, Double-blind, Proof-of-concept Study of Guselkumab in Participants with Systemic Sclerosis

Guselkumab (CNTO1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of guselkumab in participants with systemic sclerosis (SSc)	• Change from baseline in Modified Rodnan Skin Score (mRSS) at Week 24
Secondary	
• To evaluate the additional efficacy of guselkumab in participants with SSc	• Change from baseline in mRSS at Week 52 • The proportion of participants who experience worsening of mRSS at Week 24 and Week 52 • The proportion of participants achieving a score of 0.6 in American College of Rheumatology Combined Response Index in dcSSc (ACR CRISS) at Week 24 and Week 52 • Change from baseline in forced vital capacity (FVC) and percent predicted FVC at Week 24 and Week 52 • Change from baseline in the measured absolute diffusing capacity of the lung for carbon monoxide (DLCO) and the derived percent predicted DLCO at Week 24 and Week 52 • Change from baseline in digital ulcer counts at Week 24 and Week 52 • Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24 and Week 52
• To evaluate the safety and tolerability of guselkumab in participants with SSc	• Number and proportion of participants with treatment-emergent adverse events (AEs) and serious adverse events (SAEs) or adverse events of special interest (AESI) from baseline through Week 24, Week 52, Week 76 and Week 104.
• To evaluate the pharmacokinetic (PK) and immunogenicity of guselkumab	• Serum guselkumab concentrations • Incidence of anti-guselkumab antibody

Objectives	Endpoints
Exploratory	
• To evaluate the other efficacy of guselkumab in participants with SSc	• Time to disease worsening: Increase from baseline ≥5 and ≥20% in mRSS OR decrease >10% from baseline in percent predicted FVC • The proportion of participants who experience FVC decline compared with baseline at Week 24 and Week 52 • The proportion of participants who experience worsening of FVC at Week 24 and Week 52 • Change from baseline in fibrotic change assessed with high-resolution computed tomography (HRCT) at Week 24 and Week 52 in participants with baseline fibrosis/fibrotic changes • The proportion of participants who experience worsening of fibrotic change assessed with HRCT at Week 24 and Week 52 • Change from baseline in Frequency Scale for the Symptoms of Gastroesophageal reflux disease (FSSG) score at Week 24 and Week 52 • Assessment of nailfold capillaries at Week 24 and Week 52 • Change from baseline in Patient global assessment (PGA) at Week 24 and Week 52 • Change from baseline in Physician global assessment (PhGA) at Week 24 and Week 52
• To evaluate the long-term efficacy of guselkumab in participant with SSc	• Change from baseline and Week 52 in mRSS at Week 76 and Week 104 • The proportion of participants who experience worsening of mRSS at Week 76 and Week 104 • The proportion of participants achieving a score of 0.6 in American College of Rheumatology Combined Response Index in dcSSc (ACR CRISS) at Week 76 and Week 104 • Change from baseline in forced vital capacity (FVC) and percent predicted FVC at Week 76 and Week 104 • The proportion of participants who experience worsening of FVC at Week 76 and Week 104 • Change from baseline in the measured absolute diffusing capacity of the lung for carbon monoxide (DLCO) and the derived percent predicted DLCO at Week 76 and Week 104

Objectives	Endpoints
	• Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 76 and Week 104 • Change from baseline in digital ulcer counts at Week 76 and Week 104 • Change from baseline in fibrotic change assessed with high-resolution computed tomography (HRCT) at Week 76 and Week 104 in participants with baseline fibrosis/fibrotic changes • The proportion of participants who experience worsening of fibrotic change assessed with HRCT at Week 76 and Week 104 • Change from baseline in Frequency Scale for the Symptoms of Gastroesophageal reflux disease (FSSG) score at Week 76 and Week 104
• To evaluate the effect of guselkumab vs placebo on the pharmacodynamic (PD) and SSc disease biomarkers	• Change from baseline levels of skin (optional) and circulating (blood based) biomarkers over time to enable: Evaluation of target engagement in tissue/efficacy pharmacodynamic (PD) readouts • Single nucleotide polymorphisms (SNPs) frequency associated with IL-23 pathway

Hypothesis

This is a proof-of-concept (PoC) study aimed at detecting an early efficacy signal of guselkumab in participants with SSc, compared to placebo, to support further clinical development.

- The null hypothesis is that the treatment difference between guselkumab and placebo for the primary endpoint is =0.
- The alternative hypothesis is that the treatment difference between guselkumab and placebo for the primary endpoint is ≠0.

Due to the PoC nature of this study, a 2-sided alpha of 0.2 is allocated for testing this PoC hypothesis. The PoC objective will be considered met if the calculated p-value for testing this PoC hypothesis is less than 0.2.

OVERALL DESIGN

This is a randomized, double-blind, placebo-controlled, parallel, multicenter, interventional study to evaluate the efficacy of guselkumab in men and women between the ages of 18 to 75 years, inclusive, with a diagnosis of SSc according to American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2013 criteria with a disease duration of ≤36 months (defined as time from first non-Raynaud phenomenon manifestation), and mRSS ≥10 to ≤22 units.

Participants will be randomly assigned in a 1:1 ratio, based on randomization strata of presence of ILD (yes, no), baseline mRSS (low [≥10 to ≤15] or high [≥16 to ≤22]), and baseline anti-topoisomerase I antibody status (positive, negative), to one of the following treatment groups:

- Guselkumab (Group/Arm A): Guselkumab 400 mg intravenous (IV) administration at Weeks 0, 4, and 8 (induction) followed by guselkumab 200 mg subcutaneous (SC) administration every 4 weeks (Q4W) from Week 12 until Week 48 (maintenance)
- Placebo (Group/Arm B): Matching placebo IV administration at Weeks 0, 4, and 8 (induction) followed by matching placebo SC administration Q4W from Week 12 until Week 48 (maintenance)

The main study will be conducted in 3 phases: a maximum 6-week screening phase, a 52-week double-blind intervention phase, and a safety follow-up phase with a post-intervention follow-up visit at 12 weeks after the participant's last dose of study intervention to collect any AEs since the last study visit.

Participants who complete the main study (Week 0 through 52: ie, after the Week 48 evaluation, prior to Week 52 evaluation) and who, in the opinion of the investigator, may benefit from continued treatment, will participate in the LTE by signing the ICF before or at Week 52. The duration of individual participation will be approximately 66 weeks without LTE and 118 weeks with LTE.

Two planned database locks (DBLs) will occur: EOS of the main study (Week 52 visit for participants who entered LTE or safety follow up visit for participants who did not enter LTE, hereinafter referred to as "Week 52 DBL"), and EOS of LTE (Week 112 visit, hereinafter referred to as "Final DBL").

Key efficacy assessments will include mRSS, ACR CRISS score; pulmonary function tests: FVC and % of predicted FVC, and DLCO (ml/min/mm Hg) and % of predicted DLCO (hemoglobin-corrected); PhGA; and PGA. Key safety assessments include the monitoring of AEs (including SAEs, AEs of special interest [AESIs], infections, injection-site reactions, adverse events temporally associated with infusion, and hypersensitivity reactions), physical examinations, vital sign measurements, electrocardiogram (ECG) measurements, clinical laboratory tests, ILD (assessed by centrally read HRCT), and tuberculosis (TB) evaluations. Additionally, PK, biomarker, and immunogenicity assessments will also be performed in this study

NUMBER OF PARTICIPANTS

The study will target to enroll a total of approximately 56 participants with 28 participants planned per intervention group.

INTERVENTION GROUPS AND DURATION

Participants will be randomly assigned in a 1:1 ratio to 1 of the following study intervention groups:

- Guselkumab (Group/Arm A): Guselkumab 400 mg IV administration Weeks 0, 4, and 8 (induction) followed by guselkumab 200 mg SC administration Q4W from Week 12 until Week 48 (maintenance)
- Placebo (Group/Arm B): Matching placebo IV administration Weeks 0, 4, and 8 (induction) followed by matching placebo SC administration Q4W from Week 12 until Week 48 (maintenance)

During the LTE, all participants will receive guselkumab treatment in LTE as below depending on the arms they were in the main study:

- Group/Arm A (guselkumab arm from the main study): Guselkumab 200 mg SC and placebo IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100.
- Group/Arm B (placebo arm from the main study): Placebo SC and guselkumab 400 mg IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100.

The duration of individual participation will be approximately 66 weeks without LTE and 118 weeks with LTE.

EFFICACY EVALUATIONS

Efficacy assessments will include the following:

- mRSS
- ACR CRISS score
- Pulmonary function tests (PFTs):
  - FVC and % of predicted FVC
  - DLCO (ml/min/mm Hg) and % of predicted DLCO (hemoglobin-corrected)
- PhGA
- Patient-Reported Outcomes (PROs):
  - PGA
  - HAQ-DI
  - FSSG Questionnaire
- Digital ulcer assessment
- Nailfold Capillaroscopy
- Lung HRCT (centrally read)

PHARMACOKINETIC EVALUATIONS

Serum samples will be analyzed to determine concentrations of guselkumab using respective validated, specific, and sensitive methods by or under the supervision of the sponsor's respective assay methods.

IMMUNOGENICITY EVALUATIONS

Serum samples will be screened for antibodies binding to guselkumab and the titer of confirmed positive samples will be reported. Serum samples positive for anti-guselkumab antibodies will be further characterized for neutralizing antibodies (Nabs) to guselkumab. Other analyses may be performed to verify the stability of anti-guselkumab antibodies and/or further characterize the immunogenicity of guselkumab.

AUTOANTIBODIES

Samples will be collected at screening to evaluate the presence of autoantibodies (including, but not limited to anti-ribonucleic acid [RNA] polymerase, anti-centromere, and anti-topoisomerase).

PHARMACODYNAMIC AND BIOMARKER

Peripheral blood mononuclear cell (PBMC) and serum samples will be collected at timepoints specified in the Schedule of Assessments (SoA), to assess the blood cellular and molecular biomarkers to enable evaluation of target engagement in tissue/efficacy PD readouts.

An optional biomarker sub-study will obtain a biopsy sample of non-lesional (unaffected) skin sample at Week 0, and lesional (at Week 0) skin at Week 0 and 24 from all participants who consent.

PHARMACOGENOMIC EVALUATIONS

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Participant participation in pharmacogenomic research is optional.

SAFETY EVALUATIONS

Safety evaluations conducted at each study visit will include the assessment of AEs (at the visit and those occurring between evaluation visits), ILD monitoring (assessed by centrally read HRCT), TB evaluation and other infection assessments, clinical laboratory blood tests (hematology and serum chemistry including C-reactive protein), pregnancy testing, physical examinations, ECG measurements, vital signs (as defined in the Schedule of Activities), concomitant medication review, and observations for injection-site reactions, hypersensitivity reactions, and AEs temporally associated with an infusion. In addition, for participants who are eligible with surface antigen (HbsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.

STATISTICAL METHODS

Sample Size Determination

A 95% confidence interval (CI) of [−4.7, −1.7] in mRSS change from baseline to 6 months is considered a clinically meaningful change. The lower bound of this 95% CI, -4.7, has been taken as the expected treatment difference in the sample size calculation of this study, assuming guselkumab can achieve a clinically meaningful change in most of guselkumab-treated participants.

Assuming a standard deviation (SD) of 8 points, an 80% power at a 2-sided significance level of 0.20, with a 1:1 randomization ratio, to detect a treatment effect of -4.7 points, a total of at least 54 participants will be required. Allowing for up to 2 participants randomized but without post-baseline efficacy assessments, approximately 56 (28 each) randomized participants are planned.

Population for Analyses Sets

Efficacy and participant information analyses will include all randomized participants who received at least 1 dose (complete or partial) of study intervention and will be analyzed based on the randomized treatment groups, regardless of the treatment they actually received.

Safety analysis set will include all randomized participants who receive at least 1 dose (partial or complete) of study intervention and participants will be analyzed based on the treatment they receive, regardless of the treatment groups to which they are assigned.

Pharmacokinetic analysis set will include all participants who received at least 1 complete dose of guselkumab and have at least 1 observed post dose PK data.

Immunogenicity analysis set will include all participants who received at least 1 dose of guselkumab and have at least 1 observed post dose immune response data.

Efficacy Analyses

Simple descriptive summary statistics, such as n, mean, SD, median, inter quantile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

For primary endpoint (Change from baseline in mRSS at Week 24), treatment comparison will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model. The MMRM model includes treatment group, baseline mRSS, stratification factors, visit, treatment group by visit interaction, and baseline mRSS by visit interaction as fixed effects. Treatment effects will be estimated based on least-square (LS) means of the differences. The p-values for the LS mean differences along with the 2-sided 80% CI will be presented. Sensitivity and subgroup analyses for the primary endpoint will be performed, if appropriate. The details of these analyses and data handling rules will be specified in the statistical analysis plan (SAP).

All other efficacy endpoints will be summarized over time by treatment group. Treatment comparisons will be performed using an MMRM model where there are repeated continuous measurements or a logistic model where there is a dichotomous response variable. No adjustments for multiple comparisons will be made for the secondary endpoints and all p-values will be considered nominal. The detailed methods of analysis and the data-handling rules will be provided in the SAP.

Safety Analyses

Routine safety evaluations will be performed based on the safety analysis set. Adverse events, SAEs, related AEs, and AEs by severity will be summarized by treatment group. More specification of other AESIs such as ILD will be described in the SAP.

The laboratory parameters and change from baseline in selected laboratory parameters (hematology and chemistry), and the number of participants with abnormal laboratory parameters (hematology and chemistry) based on National Cancer Institute Common-Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grading will be summarized by treatment group.

Clinically relevant ECG abnormalities will be evaluated by frequency tabulations. Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

Pharmacokinetic Analyses

Unless otherwise noted, PK analyses will be based on the PK Analysis Set. Serum guselkumab concentrations over time will be summarized with descriptive statistics at each nominal sampling timepoint. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database or data presentations. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

Detailed rules for the analysis including exclusion from the PK analyses will be specified in the SAP.

Population PK modeling may be conducted when appropriate. If population PK analysis is conducted, the results will be presented in a separate report.

Immunogenicity Analyses

The incidence and titers of anti-guselkumab antibodies will be summarized for the immunogenicity analysis set. A listing of participants who are positive for anti-guselkumab antibodies will be provided. The maximum titers of anti-guselkumab antibodies will be summarized for participants who are positive for antibodies to guselkumab.

The incidence of Nabs to guselkumab will be summarized for participants who are positive for antibodies to guselkumab and have samples evaluable for neutralizing antibodies to guselkumab.

Pharmacodynamic Analyses

Serum will be collected from all subjects to assess PD markers associated with guselkumab as well as markers related to SSc. Measurements may include but are not limited to serum levels of IL-17A, IL-17F, IL-22, beta defensin-2 (BD-2), and SAA. Broader proteomic profiling (eg, via Olink method) for biomarker discovery may be performed.

Blood samples for the isolation of PBMCs will also be collected for subsequent immunophenotyping analyses by multiparameter flow cytometry or mass cytometry (CyTOF) analysis to measure immune cell populations before and during treatment. Gene expression analysis may also be performed; this may include single cell RNA-sequencing (RNA-seq) profiling.

Results of pharmacodynamic/biomarker analyses will be presented in a separate report.

Biomarkers Analyses

Characterization of gene expression changes in the skin during treatment would be analyzed as determined by RNA-seq at Weeks 0 and 24. If feasible, a non-lesional (unaffected) skin sample will be collected at Week 0; lesional (at Week 0) samples to be collected at both Weeks 0 and 24. If feasible, characterization of the tissue immunopathological changes in the skin as determined by immunohistochemistry (IHC)/ immunofluorescence (IF)/ in situ hybridization (ISH), as well as histology analysis (eg, fibrosis) may be performed. Multiparameter protein profiling (eg, imagine CyTOF) may be considered.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum concentrations of guselkumab and the efficacy measures and/or relevant PD endpoints, including biomarkers in blood or in skin biopsies, may be explored graphically when appropriate. If any visual trend is observed, additional analysis may be conducted if deemed necessary.

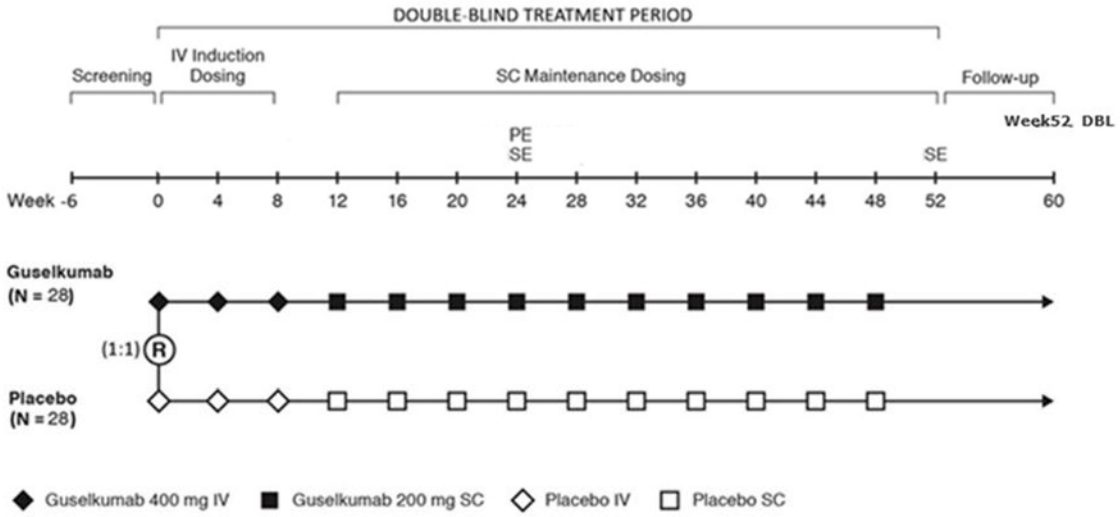
Pharmacogenomic Analyses

Genetic analysis may help to identify population subgroups that respond differently to a drug. A single DNA sample at Week 0 will be used to explore genetic factors that may influence molecular effects, clinical efficacy, or tolerability of guselkumab and to identify genetic factors associated with SSc. A locus of interest is the *IL12RB1* gene*;* a reported SSc risk allele has been identified in this gene and there is potential association with expression of the gene product (encoding a receptor for IL-23). Analysis applied to DNA samples may focus on genotyping, using molecular arrays to scan polymorphisms across the genome. Participation in the DNA sampling is optional.

Results will be presented in a separate report.

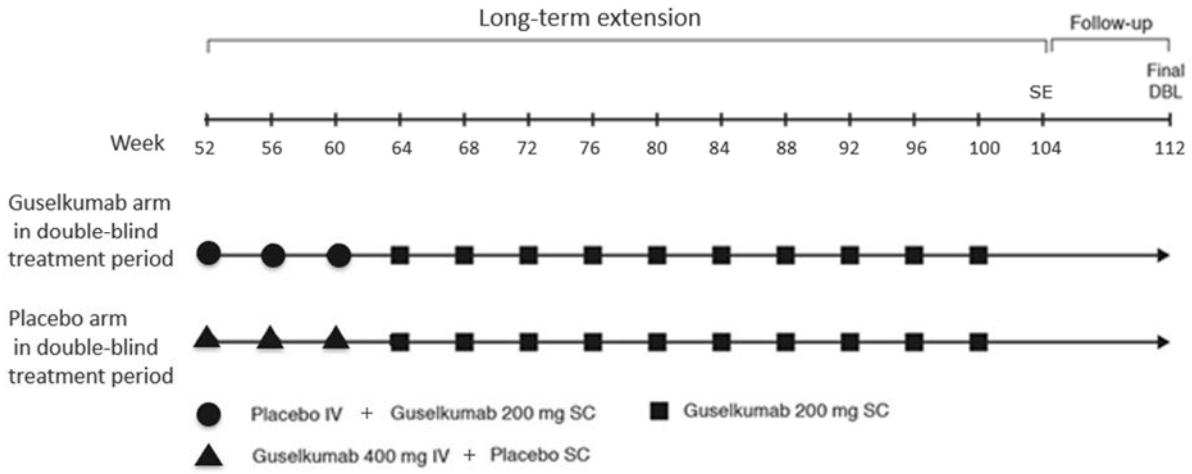
1.2. Schema

Figure 1: Schematic Overview of the Main Study



Abbreviations: DBL=database lock; IV=intravenous; N=number of participants; PE=primary endpoint; R=randomization; SC=subcutaneous; SE=secondary endpoints

Figure 2: Schematic Overview of LTE



Abbreviations: DBL=database lock; IV=intravenous; N=number of participants; PE=primary endpoint; R=randomization; SC=subcutaneous; SE=secondary endpoints

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities (SoA) of Screening and Double-Blind Study Intervention (Main Study)

Period	Screening	Double-blind Study Intervention														Safety Follow-up (EOS)[o]	Early Termination Visit (ET)
Week[h]	**-6 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**[n]	**60**	
Study Procedure																	
Screening/Administrative																	
ICF[a]	X																
ICF for optional genetic research samples	X																
ICF for participation of LTE[p]														(X)			
Medical history and demographics	X																
Inclusion/exclusion criteria[b]	X	X															
Study Intervention Administration																	
Randomization		X															
Administer study intervention		X	X	X	X	X	X	X	X	X	X	X	X	X			
Efficacy Assessments[c]																	
mRSS[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physician's global assessment		X			X			X			X				X		X
Digital ulcer assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Patient's global assessment		X			X			X			X				X		X
HAQ-DI		X			X			X			X				X		X
FSSG		X			X			X			X				X		X
Nailfold capillaroscopy		X						X							X		X
Lung HRCT (centrally read)[l]	X							X							X		
Pulmonary function tests[i]	X				X			X							X		X
ACR CRISS[m]	X				X			X							X		X
Safety Assessments																	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																
Weight	X				X			X							X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis evaluation[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X							X							X		X
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	Screening	Double-blind Study Intervention														Safety Follow-up (EOS)[o]	Early Termination Visit (ET)
Week[h]	**-6 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**[n]	**60**	
Study Procedure																	
Chest radiograph	X																
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests																	
IGRA (QuantiFERON- TB test or T-SPOT)	X																
Hepatitis B and C serology[e]	X																
HIV antibody test	X																
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry including CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Autoantibodies (including, but not limited to anti-RNA polymerase, anti-centromere, and anti-topoisomerase)[j]	X																
Pharmacokinetics and Immunogenicity																	
Serum guselkumab concentration[f]		2X	2X	2X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antibodies to guselkumab		X	X	X	X			X		X		X		X	X	X	X
Biomarkers																	
Serum biomarkers		X	X		X	X		X	X					X			X
PBMCs		X	X					X						X			X
Skin biopsy (optional)		X						X									
Pharmacogenomics (optional)[d]																	
Blood sample collection for DNA (EDTA tube)		X															
Blood sample collection for RNA (PAXgene tube)		X	X					X									

Abbreviations: CRP=C-reactive protein; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EDTA= ethylenediaminetetraacetic acid; EOS= end-of-study; ET=early termination; FSSG= Frequency Scale for the Symptoms of Gastroesophageal reflux disease; HAQ-DI= Health Assessment Questionnaire-Disability Index; HIV= human immunodeficiency virus; HRCT= high resolution computed tomography; ICF=informed consent form; IGRA= interferon gamma release assays; LTE=

long-term extension, mRSS= modified Rodnan skin score; PBMC= Peripheral blood mononuclear cells; PRO=patient-reported outcome; RNA=ribonucleic acid; SoA=schedule of assessments

Footnotes:

a. Must be signed before first study-related activity.
b. Minimum criteria for the availability of documentation supporting the eligibility criteria will be described in the full protocol. Check clinical status again before first dose of study medication.
c. All PRO assessments should be conducted before other assessments in the order listed in the above SoA table.
d. The pharmacogenomic sample should be collected at the specified time points, but it may be collected at a later time point without constituting a protocol deviation.
e. For participants who are eligible with surface antigen (HbsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.
f. For all visits where study intervention will be administered, 1 blood sample should be collected prior to study intervention administration for evaluation of serum concentrations and/or antibodies to study intervention. In addition, for IV infusion-related visits (Week 0, 4, 8), another blood draw should be taken approximately 60 minutes after the completion of the IV infusion for serum concentration measurement.
g. mRSS must be assessed by the same investigator longitudinally throughout the study
h. Screening should occur within 6 weeks prior to W0 visit. The study visit week are indicated and calculated based on the day of randomization/first administration of the study intervention (W0 visit). Visit window should be ±7 days for each visit (Visit window for W0 visit should be -7 days).
i. Pulmonary function tests include forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). If decline in % predicted FVC ≥ 15 % (relative) is seen, another FVC test needs to be performed within a month.
j. To be measured at a central laboratory
k. Participants with potential active tuberculosis need to pause the study intervention administration until the tuberculosis assessment is completed.
l. For participants with stent, HRCT cannot be centrally read.
m. For screening, information on ACR CRISS step 1 will be collected as SSc Condition of Interest.
n. For participants who will NOT enter LTE, refer to Week 52 in Table 1. For participants who will enter LTE, refer to Week 52 and the subsequent visits in Table 2.
o. Only participants who will NOT enter LTE should perform the safety follow up visit at Week 60.
p. ICF for participation of LTE should be obtained at the latest at Week 52.

Table 2: Long-Term Extension for Eligible Participants Who Have Completed the Main Study (LTE)

Period	Long-term extension (LTE)														Safety Follow-up (LTE-EOS)	Early Termination Visit (LTE-ET)
LTE Week[a]	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**112**	
Study Procedure																
Administrative																
ICF for participation of LTE[b]	(X)															
Study Intervention Administration																
Administer study intervention[c]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Training for self-administration[d] (Optional)		X	X	X	⇢	⇢	⇢	⇢	⇢	⇢	⇢	→				
At-home administration[e] (Optional)									X		X		X			
Efficacy Assessments[f]																
mRSS[g]	X	X	X	X	X	X	X	X		X		X		X		X
Physician's global assessment	X			X			X			X				X		X
Digital ulcer assessment	X			X			X			X				X		X
Patient's global assessment	X			X			X			X				X		X
HAQ-DI	X			X			X			X				X		X
FSSG	X			X			X			X				X		X
Nailfold capillaroscopy	X															
Lung HRCT (centrally read)[h]	X						X							X		
Pulmonary function tests[i]	X			X			X							X		X
ACR CRISS	X			X			X							X		X
Safety Assessments[j]																
Physical examination	X	X	X	X	X	X	X	X		X		X		X	X	X
Weight	X			X			X							X		X
Vital signs	X	X	X	X	X	X	X	X		X		X		X	X	X
Tuberculosis evaluation[k]	X	X	X	X	X	X	X	X		X		X		X	X	X
12-lead ECG	X						X							X		X
Urine pregnancy test	X	X	X	X	X	X	X	X		X		X		X	X	X
Concomitant therapy[l]	X	X	X	X	X	X	X	X	⇢	X	⇢	X	⇢	X	X	X
Adverse Events[l]	X	X	X	X	X	X	X	X	⇢	X	⇢	X	⇢	X	X	X
Clinical Laboratory Tests																
Hematology	X	X	X	X	X	X	X	X		X		X		X	X	X
Chemistry including CRP	X	X	X	X	X	X	X	X		X		X		X	X	X

Period	Long-term extension (LTE)														Safety Follow-up (LTE-EOS)	Early Termination Visit (LTE-ET)
LTE Week[a]	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**112**	
Study Procedure																
Urinalysis	X	X	X	X	X	X	X	X		X		X		X	X	X
Pharmacokinetics and Immunogenicity																
Serum guselkumab concentration[m]	X	X	X	X			X			X		X		X	X	X
Antibodies to guselkumab	X	X	X	X			X			X		X		X	X	X

Abbreviations: CRP=C-reactive protein; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EOS= end-of-study; ET=early termination; FSSG= Frequency Scale for the Symptoms of Gastroesophageal reflux disease; HAQ-DI= Health Assessment Questionnaire-Disability Index; HIV= human immunodeficiency virus; HRCT= high resolution computed tomography; ICF=informed consent form; LTE= long-term extension; mRSS= modified Rodnan skin score; PRO=patient-reported outcome; SoA=schedule of assessments

Footnotes:

a. Visit window should be ±7 days for each visit.
b. IC for participation of LTE should be obtained at least the first assessments at Week 52.
c. Self-administration can begin from LTE Week 68 visit according to the regional/local regulations and instruction at the discretion of the investigator and participant, and upon completion of 3 times training.
d. Three times trainings are required prior to begin self-administration, and participants can start the training at any time after Week 56.
e. For study participants who are trained to self-inject at home, study participants will be trained to perform self-evaluation for injection-site reactions and reporting of AEs after administering the study intervention at home. Participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding. Participants will record all at-home study intervention administrations on a diary card.
f. All PRO assessments should be conducted in the order listed in the above SoA table.
g. mRSS must be assessed by the same investigator longitudinally throughout the study.
h. For participants with stent, HRCT cannot be centrally read.
i. Pulmonary function tests include forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). If decline in FVC% predicted ≥15% (relative) is seen, another FVC test needs to be performed within a month.
j. For participants who are eligible with surface antigen (HbsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.
k. Participants with potential active tuberculosis need to pause the study intervention administration until the tuberculosis assessment is completed.
l. If participants come to the clinical site for study intervention at following visits; LTE Week 84, 92 and 100, site staff should confirm if there is any change of concomitant therapies and adverse events. If necessary, safety assessments and clinical laboratory test can be performed as an unscheduled assessment.
m. 1 blood sample should be collected prior to study intervention administration for evaluation of serum concentrations and/or antibodies to study intervention.

2. INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by a thickening and tightening of the skin and involvement of internal organs (gastrointestinal tract, heart, lungs, and kidneys) with a chronic and frequently progressive course. One of the clinical features of SSc is its patient-to-patient variability, and heterogeneity has been observed in clinical manifestations, autoantibody profiles, disease progression, response to treatment, and survival. On the basis of the extent of their skin involvement, patients are grouped into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) subsets. In lcSSc, skin fibrosis is restricted to the fingers (sclerodactyly), distal extremities, and face. On the other hand, patients with dcSSc have skin fibrosis in areas including trunk and proximal extremities, relatively rapid disease progression with extensive skin changes and early development of visceral organ complications compared to lcSSc. Systemic sclerosis is designated as an intractable disease in Japan and the number of moderate to severe SSc patients was 26,740 in 2018 according to the Japan Intractable Diseases Information Center. The prevalence of SSc ranged from 7-489/million and the incidence from 0.6-122/million/year worldwide (Chiffot 2007).

Systemic sclerosis has high disease burden and unmet medical needs due to the limited efficacy of most current treatments. No drugs significantly influence the natural course of SSc and no advanced treatment is approved for the treatment of overall SSc. Autologous hematopoietic stem cell transplantation (HSCT) trials in dcSSc have demonstrated survival benefit including meaningful improvement in skin, lung fibrosis, and health-related quality of life. These benefits, however, must be weighed against the increased risk of transplant-related mortality, which limits wider use of HSCT in the treatment for SSc.

Survival has improved in recent decades and correlates best with the clinical disease subtype (dcSSc vs lcSSc) and with the extent of organ involvement. Five-year survival among patients with dcSSc has improved significantly, from 69% in the 1990-1993 cohort to 84% in the 2000-2003 cohort. Five-year survival among the patients with lcSSc remained very high and unchanged for the same periods (93% and 91%, respectively) (Nihtyanova 2010).

Mortality associated with scleroderma renal crisis has declined significantly during the last decades, as use of angiotensin-converting enzyme inhibitors. In contrast, pulmonary involvement (ILD and/or pulmonary arterial hypertension) has become the most common cause of death in patients with SSc. Contrary to rheumatoid arthritis (RA), the concept and use of disease-modifying therapies that attenuate or reverse pathology and clinical impact are not currently applied to SSc.

Various drugs are used to treat specific symptoms or organ systems. Low dose corticosteroids may be helpful for skin tightening of acute progressive patients but may predispose to renal crisis and thus are used only if necessary. Nintedanib, a tyrosine kinase inhibitor was approved for the treatment of ILD associated with SSc. Various immunosuppressants, including methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide, may help pulmonary alveolitis. Mycophenolate mofetil is also effective for the treatment of ILD. Prostacyclin and endothelin receptor antagonists are used for pulmonary hypertension. Calcium-channel blockers may help

Raynaud phenomenon. Intravenous (IV) infusions of prostaglandin E1 or prostacyclin or sympathetic blockers can be used for digital ischemia. Reflux esophagitis is relieved by proton pump inhibitors.

While the variety of medications are used to treat some of the SSc symptoms, there are still high unmet medical needs for disease-modifying therapies with unequivocal efficacy and safety profile for SSc.

Guselkumab (CNTO1959) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high specificity and affinity. The binding of guselkumab to the IL-23p19 subunit blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation, and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

Guselkumab has been approved for the treatment of adults with moderate to severe plaque psoriasis (PsO) in the United States (US), European Union, Canada, Japan and several other countries worldwide, and for the treatment of psoriatic arthritis (PsA) in US, Canada, Brazil, and Japan. In addition, guselkumab has been approved for the treatment of generalized pustular PsO, erythrodermic PsO, and palmoplantar pustulosis in Japan.

Guselkumab is currently being developed worldwide in other diseases including for the treatment of patients with PsA, hidradenitis suppurativa (HS), familial adenomatous polyposis, Crohn's disease (CD), lupus nephritis (LN), ulcerative colitis (UC), and giant cell arteritis (GCA). A Phase 3 study in PsA, a Phase 2/3 program in CD, a Phase 2b/3 study in UC, and Phase 2 studies in HS, LN, and GCA are currently ongoing or planned globally.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure (IB) for guselkumab. (IB guselkumab 2020)

The term "study intervention" throughout the protocol, refers to guselkumab and placebo as defined in Section 6.1, Study Intervention(s) Administered.

The term "sponsor" used throughout this document refers to the entities listed in the 'Protocol Supplementary Information', which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

While the pathogenesis of SSc is complex and multifactorial, accumulated evidence suggests that IL23/IL-17 pathway is involved in the pathophysiology of SSc. Several clinical studies have shown that serum IL-23/IL-17 and skin IL-23 are increased in SSc patients compared with healthy volunteers (Komura 2008; Kurasawa 2000). Correlation between serum IL-23 levels and severity/extent of interstitial lung involvement was observed in patients with SSc (Rolla 2016). In addition, internal analysis of ribonucleic acid (RNA)-sequencing (RNA-seq) data obtained from

recent onset SSc patient skin samples indicated upregulation of IL-23/IL17 related genes (analysis from global Translational Science Medicine team). A case report has shown that ustekinumab (mAb against IL-12 and IL-23) successfully improved skin tightening in a patient with both psoriasis and SSc (Ichihara 2017). There is an ongoing Phase 3 clinical trial to evaluate brodalumab, IL-17R antibody in subjects with SSc in Japan (NCT03957681). Although the results of preceding brodalumab Phase 1b study (n 8) (NCT04368403) has not been publicly available, efficacy and safety outcome of the Phase 1 study was evaluated and currently ongoing Phase 3 study was initiated.

These results suggest that reducing IL-23-mediated inflammation with guselkumab may improve the signs and symptoms of active SSc. Taken together, these observations provide sufficient rationale to explore the role of IL-23 in the pathogenesis of SSc in this proof-of-concept (PoC) study of guselkumab in participants with SSc.

2.2. Background

Nonclinical Studies

A comprehensive overview of the nonclinical development program for guselkumab to support the initiation of the study has been completed and the information is available in Section 3 of the latest version of the guselkumab IB (IB guselkumab 2020).

Details regarding the proposed dose regimen and dose rationale are described in Section 6.1 and Section 4.3.

Clinical Studies

As of 12 July 2020, 31 clinical studies of guselkumab have been completed or are ongoing. An estimated 348 healthy subjects, 4,034 subjects with PsO, 109 subjects with RA, 1,471 subjects with PsA, 182 subjects with palmoplantar pustulosis, 230 subjects with CD, 173 subjects with HS, 117 subjects with UC, and 19 subjects with familial adenomatous polyposis have been exposed to guselkumab. Overall, an estimated 6,683 subjects have been exposed to guselkumab in the clinical development program.

The largest clinical experience to date with guselkumab has been in PsO. The safety profile of guselkumab in subjects with moderate to severe PsO is based on data from the Phase 2 study CNTO1959PSO2001 and Phase 3 studies CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSO3003, CNTO1959PSO3006, and CNTO1959PSO3009. Of the 2,711 guselkumab-treated subjects, 2,255 subjects were exposed for at least 1 year, 1,516 were exposed for at least 2 years, and 692 subjects and were exposed for 3 years. Long-term extensions of 2 of the studies (CNTO1959PSO3001 and CNTO1959PSO3002) are ongoing and will continue through up to 5 years of follow-up.

This section provides a summary of the sponsor's assessment of how the overall clinical experience with guselkumab across various indications supports the investigation of guselkumab in SSc. Details about these guselkumab clinical development programs across various indications are provided in Section 4 of the latest version of the guselkumab IB (IB guselkumab 2020).

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of guselkumab may be found in the IB.

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Clinical worsening of systemic sclerosis (SSc)	The benefit-risk of guselkumab in the treatment of SSc has not been established.	Participants will discontinue study intervention if it is not in their best interest or if they need to initiate protocol-prohibited medications including certain biologics (Section 6.8 and Section 7.1).
Potential Risks Due to Study Intervention Guselkumab		
Serious infections and reactivation of latent infections	Available animal and human data suggest that blockade of IL-23 may be associated with an increased infection risk.	• Participants with a history of, or ongoing, chronic or recurrent infectious disease, including human immunodeficiency virus (HIV), Hepatitis B or C, will be excluded from the study. Similarly, participants with evidence of active or untreated latent tuberculosis (TB) will be excluded from the study (Section 5.2). • Participants who have received Bacille Calmette-Guérin (BCG) vaccination within 12 months or any other live viral or bacterial vaccination within 12 weeks from randomization will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention. • Participants will be instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators are instructed in the protocol to monitor for signs or symptoms of infections, including TB (Section 8.2.9 and Section 8.2.10). • Discontinuation of a participant's study intervention must be strongly considered if the participant develops a serious infection, including but

		not limited to sepsis or pneumonia. In addition, any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete (Section 8.2.10).
Hypersensitivity reactions, including serious hypersensitivity reactions.	Serious hypersensitivity reactions including anaphylaxis have been reported in postmarketing experience with guselkumab in psoriasis patients.	• Participants with known allergy, hypersensitivity, or intolerance to guselkumab or its excipients will be excluded from the study. • Sites are instructed that before any administration of study intervention, appropriately trained personnel and medications (eg, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. In addition, all participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension) (Section 8.2.8). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1).
Malignancy	The preponderance of preclinical data suggests that blockade of endogenous interleukin (IL)-23 would not be detrimental and may in fact be beneficial in tumor immunosurveillance and host protection; however, a risk of malignancy cannot be excluded.	• Those participants who currently have a malignancy or have a history of malignancy within 5 years prior to screening (with exceptions noted in Section 5.2) will be excluded from the study. Additionally, participants who have a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly will be excluded from the study (Section 5.2). • During the conduct of the study, participants will undergo regular clinical monitoring including routine safety laboratory tests to assess for any changes in health

		status that may indicate a possible malignancy. • Participants who develop a malignancy during the study (with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1).
Liver injury	A serious adverse event (SAE) of 'toxic hepatitis' was reported in the ongoing Phase 2/3 guselkumab Crohn's disease program in a participant who received guselkumab 1200 mg intravenous (IV) at Weeks 0, 4, and 8, and 200 mg subcutaneous (SC) at Week 12. Based on the hepatocellular pattern of injury, temporal relationship of the event to guselkumab exposure, and the exclusion of alternative etiologies, this event may represent drug-induced liver injury possibly related to guselkumab. Alanine aminotransferase (ALT)/ aspartate aminotransferase AST abnormailities are a known risk for guselkumab, and that in the psoriatic arthritis studies, patients receiving guselkumab every 4 weeks (Q4W) were more likely to experience transaminase elevations than those receiving it every 8 weeks (Q8W).	• During the conduct of the study, liver function tests will be monitored at regular intervals in accordance with regulatory guidance (FDA 2009). In addition, the induction doses evaluated in this clinical program will not exceed 400 mg IV. • Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg, jaundice), should undergo a thorough investigation for possible causes of liver injury. A participant must have their study intervention discontinued if the participant has severe liver test abnormalities that are not transient and are not explained by other etiologies (Section 7.1 and Section 10.6).
Immunosuppression	It is unknown if guselkumab in combination with other immunosuppressives increases the risk of diseases associated with immunosuppression, such as infections or malignancy.	• In order to minimize the theoretical increased risk of infection or malignancy with the combination of guselkumab with immunosuppressive therapy, the baseline dose of oral corticosteroids on study entry is limited ≤10 mg of prednisolone or equivalent per day which must be at a stable dose ≥4 weeks prior to first dose of study intervention. Furthermore, participants receiving investigational or approved immunomodulatory agents like IL-23 inhibitor therapy, IL-12/23 inhibitors, or IL-17 inhibitors, failed for efficacy in SSc or within 12 weeks or 5 half-lives

		(whichever is longer) of first administration of the study intervention, are excluded from the study. Additionally, participants are also excluded from the study if they have received IL-receptor inhibitors (eg, Tocilizumab, sarilumab) or tyrosine kinase inhibitors (eg, Nintedanib) within 12 weeks or 5 half-lives (whichever is longer) or anti-cluster of differentiation 20 (anti-CD20) antibodies (eg, Rituximab) within 1 year or 5 half-lives (whichever is longer) prior to first administration of the study intervention. Further details regarding concomitant medications is provided in Section 5.1 and Section 5.2. • During study participation, the use of IL-23 inhibitor therapy, IL-12/23 inhibitors, IL-17 inhibitors, tocilizumab, sirukumab, sarilumab, mavrilimumab, abatacept, belimumab, or tyrosine kinase inhibitors is prohibited. Participants initiating these treatments will be discontinued from further study intervention administration (Section 7.1).

2.3.2. Benefits for Study Participation

The efficacy and safety of guselkumab in the treatment of SSc has not been established. The scientific and clinical rationale for IL-23 blockade in the treatment of SSc supports the clinical evaluation of guselkumab in this disease population

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with guselkumab are justified by the anticipated benefits that may be afforded to participants with SSc.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of guselkumab in participants with systemic sclerosis (SSc)	• Change from baseline in Modified Rodnan Skin Score (mRSS) at Week 24
Secondary	
• To evaluate the additional efficacy of guselkumab in participants with SSc	• Change from baseline in mRSS at Week 52 • The proportion of participants who experience worsening of mRSS at Week 24 and Week 52 • The proportion of participants achieving a score of 0.6 in American College of Rheumatology Combined Response Index in dcSSc (ACR CRISS) at Week 24 and Week 52 • Change from baseline in forced vital capacity (FVC) and percent predicted FVC at Week 24 and Week 52 • Change from baseline in the measured absolute diffusing capacity of the lung for carbon monoxide (DLCO) and the derived percent predicted DLCO at Week 24 and Week 52 • Change from baseline in digital ulcer counts at Week 24 and Week 52 • Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24 and Week 52
• To evaluate the safety and tolerability of guselkumab in participants with SSc	• Number and proportion of participants with treatment-emergent adverse events (AEs) and serious adverse events (SAEs) or adverse events of special interest (AESI) from baseline through Week 24, Week 52, Week 76 and Week 104
• To evaluate the pharmacokinetic (PK) and immunogenicity of guselkumab	• Serum guselkumab concentrations • Incidence of anti-guselkumab antibody
Exploratory	
• To evaluate the other efficacy of guselkumab in participants with SSc	• Time to disease worsening: Increase from baseline ≥5 and ≥20% in mRSS OR decrease >10% from baseline in FVC % • The proportion of participants who experience FVC decline compared with baseline at Week 24 and Week 52 • The proportion of participants who experience worsening of FVC at Week 24 and Week 52 • Change from baseline in fibrotic change assessed with high-resolution computed tomography (HRCT) at Week 24 and Week 52 in participants

Objectives	Endpoints
	with baseline fibrosis/fibrotic changes • The proportion of participants who experience worsening of fibrotic change assessed with HRCT at Week 24 and Week 52 • Change from baseline in Frequency Scale for the Symptoms of Gastroesophageal reflux disease (FSSG) score at Week 24 and Week 52 • Assessment of nailfold capillaries at Week 24 and Week 52 • Change from baseline in Patient global assessment (PGA) at Week 24 and Week 52 • Change from baseline in Physician global assessment (PhGA) at Week 24 and Week 52
• To evaluate the long-term efficacy of guselkumab in participant with SSc	• Change from baseline and Week 52 in mRSS at Week 76 and Week 104 • The proportion of participants who experience worsening of mRSS at Week 76 and Week 104 • The proportion of participants achieving a score of 0.6 in American College of Rheumatology Combined Response Index in dcSSc (ACR CRISS) at Week 76 and Week 104 • Change from baseline in forced vital capacity (FVC) and percent predicted FVC at Week 76 and Week 104 • The proportion of participants who experience worsening of FVC at Week 76 and Week 104 • Change from baseline in the measured absolute diffusing capacity of the lung for carbon monoxide (DLCO) and the derived percent predicted DLCO at Week 76 and Week 104 • Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 76 and Week 104 • Change from baseline in digital ulcer counts at Week 76 and Week 104 • Change from baseline in fibrotic change assessed with high-resolution computed tomography (HRCT) at Week 76 and Week 104 in participants with baseline fibrosis/fibrotic changes • The proportion of participants who experience worsening of fibrotic change assessed with HRCT at Week 76 and Week 104

Objectives	Endpoints
	• Change from baseline in Frequency Scale for the Symptoms of Gastroesophageal reflux disease (FSSG) score at Week 76 and Week 104
• To evaluate the effect of guselkumab vs placebo on the pharmacodynamic (PD) and SSc disease biomarkers	• Change from baseline levels of skin (optional) and circulating (blood based) biomarkers over time to enable: Evaluation of target engagement in tissue/efficacy pharmacodynamic (PD) readouts • Single nucleotide polymorphisms (SNPs) frequency associated with IL-23 pathway

Refer to Section 8, STUDY ASSESSMENTS AND PROCEDURES for evaluations related to endpoints.

HYPOTHESIS

This is a PoC study aimed at detecting an early efficacy signal of guselkumab in participants with SSc, compared to placebo, to support further clinical development.

- The null hypothesis is that the treatment difference between guselkumab and placebo for the primary endpoint is 0.
- The alternative hypothesis is that the treatment difference between guselkumab and placebo for the primary endpoint is ≠0.

Due to the PoC nature of this study, a 2-sided alpha of 0.2 is allocated for testing this PoC hypothesis. The PoC objective will be considered met if the calculated p-value for testing this PoC hypothesis is less than 0.2.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel, multicenter, interventional study to evaluate the efficacy of guselkumab in men and women between the ages of 18 to 75 years, inclusive, with a diagnosis of SSc according to American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2013 criteria with a disease duration of ≤36 months (defined as time from first non-Raynaud phenomenon manifestation), and Modified Rodnan Skin Score (mRSS) of ≥10 to ≤22 units.

For the main study, participants will be randomly assigned in a 1:1 ratio, based on randomization strata of presence of ILD (yes, no), baseline mRSS (low [≥10 to ≤15] or high [≥16 to ≤22]), and baseline anti-topoisomerase I antibody status (positive, negative), to 1 of the following treatment groups:

- Guselkumab (Group/Arm A): Guselkumab 400 mg IV administration at Weeks 0, 4, and 8 (induction) followed by guselkumab 200 mg subcutaneous (SC) administration every 4 weeks (Q4W) from Week 12 until Week 48 (maintenance)
- Placebo (Group/Arm B): Matching placebo IV administration at Weeks 0, 4, and 8 (induction) followed by matching placebo SC administration Q4W from Week 12 until Week 48 (maintenance)

The main study will be conducted in 3 phases: a maximum 6-week screening phase, a 52-week double blind intervention phase, and a safety follow-up phase with a post-intervention follow-up visit at 12 weeks after the participant's last dose of study intervention to collect any adverse events (AEs) since the last study visit. The duration of individual participation will be approximately 66 weeks.

Participants who complete the main study (Week 0 through 52: ie, after the Week 48 evaluation, prior to Week 52 evaluation) and who, in the opinion of the investigator, may benefit from continued treatment, will participate in the LTE by signing the ICF before or at Week 52. The duration of individual participation will be approximately 66 weeks without LTE and 118 weeks with LTE. The detail is provided in Section 4.1.1 Long-term Extension. During the LTE, Self-Administration will be allowed for participants who complete training. Refer to Section 4.1.2 Self-Administration of Study Intervention.

Two planned database locks (DBLs) will occur: EOS of the main study (Week 52 visit for participants who entered LTE or safety follow up visit for participants who did not enter LTE, hereinafter referred to as "Week 52 DBL"), and EOS of LTE (Week 112 visit, hereinafter referred to as "Final DBL").

Key efficacy assessments will include mRSS, American College of Rheumatology Combined Response Index in dcSSc (ACR CRISS) score; pulmonary function tests: forced vital capacity (FVC) and % of predicted FVC, and diffusing capacity of the lung for carbon monoxide (DLCO) (ml/min/mm Hg) and % of predicted DLCO (hemoglobin-corrected); physician global assessment (PhGA); and patients global assessment (PGA) (refer to Section 8.1, Efficacy Assessments). Key safety assessments include the monitoring of AEs (including serious adverse events [SAEs], adverse events of special interest [AESIs], infections, injection-site reactions, AEs temporally associated with infusion, and hypersensitivity reactions), physical examinations, vital sign measurements, electrocardiogram (ECG) measurements, clinical laboratory tests, ILD monitoring (assessed by centrally read high-resolution computed tomography [HRCT]), and TB evaluations (refer to Section 8.2, Safety Assessments). Additionally, PK, biomarker, and immunogenicity assessments will also be performed in this study.

A target of 56 participants will be randomly assigned in this study with 28 participants planned per intervention group.

An optional biomarker sub-study will obtain a biopsy sample of non-lesional (unaffected) skin sample at Week 0, and lesional (at Week 0) skin at Week 0 and 24 from all participants who consent.

A diagram of the study design is provided in Section 1.2. Schema.

4.1.1. Long-term Extension

The objective of LTE is to evaluate the long-term safety and efficacy of guselkumab in SSc patients. The LTE begins with the completion of the assessments at the Week 52, and LTE continues through LTE Week 104. The LTE includes a safety follow-up phase with a post-intervention follow-up visit at LTE Week 112 (12 weeks after the participant's last dose of study intervention).

Participants who complete the main study and who, in the opinion of the investigator, may benefit from continued treatment, will participate in the LTE by signing the ICF before or at Week 52, will receive guselkumab treatment in LTE as below depending on the arms they were in the main study (Week 0 through 52).

- Group/Arm A (guselkumab arm from the main study): Guselkumab 200 mg SC and placebo IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100.
- Group/Arm B (placebo arm from the main study): Placebo SC and guselkumab 400 mg IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100.

During the LTE, all protocol-allowed concomitant medications and rescue medications may be administered at the discretion of the investigator. Prohibited medications listed in Section 6.1 continue to be prohibited in the LTE.

All study evaluations to be performed during the LTE are listed in the Section 1.3 Schedule of Activities (SoA).

The study blind will be maintained until the Week 52 DBL and participants will continue to receive study intervention in a blinded manner at all visits until that time.

The final DBL will occur when all participants complete the LTE (EOS for LTE period).

At selected visits during the LTE, at the discretion of the investigator and participant, and after appropriate and documented training, participants will self-administer study intervention. Details are provided in Section 4.1.2 Self-Administration of Study Intervention.

A diagram of the study design is provided in Section 1.2. Schema.

4.1.2. Self-Administration of Study Intervention

From the LTE, all participants who are willing to perform self-study intervention administration can receive training on how to self-administer study intervention at the investigative site. Three times trainings are required, and participants can start the training at any time after Week 56.

At-home administration can begin from the selected visit according to regional/local regulations and instruction at the discretion of the investigator and participant, and upon completion of training.

Participants who are eligible for self-intervention administration will be supplied with study intervention for at-home administration at Week 80 and will have the first at-home administration at Week 84. At-home administration can only be performed for the following visits (if applicable): LTE Weeks 84, 92, and 100. Participants will record all at-home study intervention administrations on a diary card. Participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding. Finally, participants will continue to have study visits and assessments at the investigative sites through LTE, as outlined in Section 1.3.

Participants who are unable or unwilling to have injections administered away from the site will be required to return to the site for administration of study intervention.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the PK, immunogenicity, pharmacodynamic (PD), efficacy, safety, or tolerability of guselkumab and to identify genetic factors associated with SSc.

Biomarker samples will be collected to evaluate the mechanism of action of or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the PD of guselkumab and aid in evaluating the intervention-clinical response relationship.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be

withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected (up to 413 mL per participant through Week 52, and up to 567 mL per participant through Week 112) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the blood donation rule by the Japanese Red Cross Society.

4.3. Justification for Dose

The following guselkumab dose regimen will be evaluated through Week 48:

- Induction: 400 mg IV at Weeks 0, 4, and 8
- Maintenance: 200 mg SC Q4W starting from Week 12

The guselkumab dose regimen for this Phase 2 study was selected based on the objective of determining the efficacy of guselkumab for treatment of SSc with possibly maximum drug exposure accompanied with no safety concerns based on benefit-risk profile of available guselkumab clinical trial data.

The proposed choice of an IV induction dose of 400 mg guselkumab at Weeks 0, 4 and 8 follows the typical induction-maintenance treatment approach that has been used for investigative studies of guselkumab in inflammatory diseases with target tissue that is more difficult to penetrate (eg, CD). Induction therapy is essential to control and reduce the inflammatory damage and the maintenance therapy is important to stabilize disease activity of SSc. This dosing regimen aims for complete target inhibition of IL-23 in the affected organs including skin in this PoC study.

Data from the ongoing guselkumab Phase 2/3 study with CD patients were considered in the selection of the guselkumab IV induction dose regimens in this Phase 2 SSc study. In the Phase 2 CD dose-ranging study, 3 guselkumab IV induction doses of 200, 600, and 1200 mg IV Q4W were assessed while in the Phase 2/3 UC study, 200 mg and 400 mg IV induction doses are being evaluated. A Dose Selection Committee reviewed the unblinded Week 12 interim analysis of efficacy, safety, PK, and PD data and recommended an induction dose of 200 mg IV for the Phase 3 CD study. However, since UC may need a higher induction dose as patients with UC may have higher inflammatory burden and a “leakier” gut leading to increased drug clearance, the 400 mg IV Q4W induction dose regimen was also selected for the Phase 2/3 UC study. In consideration of induction dose for other inflammatory diseases, the 400 mg IV Q4W induction dose regimen was selected for this Phase 2 SSc study in order to increase the opportunity of obtaining the maximum clinical response.

The safety of 200 mg and 600 mg IV Q4W regimens in the Phase 2b CD study was acceptable. A single case of potential drug-induced liver injury possibly related to guselkumab was reported in a participant who received the guselkumab 1200 mg IV dose regimen. Compared to the guselkumab 1200 mg IV dose previously investigated in CD, the guselkumab 400 mg IV dose would provide an approximately 3-fold lower exposure. In addition, the predicted exposure margin

for 400 mg IV relative to the no observed adverse event level (NOAEL) of 50 mg/kg/week in cynomolgus monkeys is approximately 10- to 13-fold, which is considered adequate to support the limited duration of IV dosing (ie, 3 doses over 12 weeks).

Guselkumab 200 mg SC Q4W was selected as the maintenance dose regimen for this study with the goal of increasing the opportunity of obtaining the maximum clinical response for SSc. This dose regimen is lower than the 400 mg IV dose regimen, taking into account dose level, dosing frequency, and the SC bioavailability of approximately 50% (as reported in a Phase 1 study in healthy subjects [refer to IB guselkumab 2020]).

With respect to safety of the maintenance dose regimens, the predicted exposure margins for the 200 mg SC Q4W dose regimen relative to the NOAEL of 50 mg/kg/week in cynomolgus monkeys are approximately 33 to 40, which is considered adequate to support the long-term SC dosing (for chronic maintenance) in the guselkumab SSc clinical development programs. Guselkumab is approved for the treatment of plaque PsO with a good long-term clinical safety profile (with data generated primarily at 100 mg SC Q8W), and dose regimens as high as 200 mg SC Q8W have been shown to have favorable safety in a 6-month Phase 2 trial in RA and a 1-year Phase 3 trial in subjects with PPP in Japan.

The available clinical safety data, along with acceptable safety margins and other studies evaluating similar dose regimens from other ongoing studies, make it reasonable to study SSc with this dose regimen.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant who will NOT enter LTE will be considered to have completed the main study if he or she has completed all the assessments at Week 52 of the double-blind phase and completed the final safety follow-up visit (EOS).

A participant who will enter LTE will be considered to have completed the main study if he or she has completed all the assessments at Week 52 of the double-blind phase, and the participant will be considered to have completed the LTE study if he or she has completed all the assessments at LTE Week 104 and completed the final safety follow-up visit (LTE-EOS).

Participants who prematurely discontinue study intervention for any reason before completion of the double-blind phase and LTE can be considered to have completed the study if they have completed all the assessments at early termination visit and completed the final safety follow-up visit.

5. STUDY POPULATION

Screening for eligible participants will be performed within 6 weeks before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Male or female (according to their reproductive organs and functions assigned by chromosomal complement).

2. 18 to 75 years of age, inclusive.

Type of Participant and Disease Characteristic

3. Medically stable on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. Any abnormalities, must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.

4. Medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel including liver enzymes, blood coagulation, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.

5. Diagnosis of SSc according to ACR and EULAR 2013 criteria.

6. Diffuse cutaneous SSc according to the LeRoy criteria ie, skin fibrosis proximal to the elbows and knees in addition to acral fibrosis.

7. Disease duration of ≤36 months (defined as time from first non-Raynaud phenomenon manifestation).

8. ≥ 10 and ≤22 mRSS units at screening and Week 0.

9. FVC ≥60% of predicted at screening.

10. DLCO ≥40% of predicted (hemoglobin-corrected) at screening.

11. Participants who meet 1 of the following criteria at screening:

    a) Increase of ≥3 mRSS units, compared with an assessment performed within the previous 2 to 6 months.*

    b) Involvement of 1 new body area with an increase of ≥2 mRSS units compared with an assessment performed within the previous 2 to 6 months.*

    c) Involvement of 2 new body areas with increase of ≥1 mRSS units compared with the assessment within the previous 2 to 6 months.*

    *Excluding participants with decrease in mRSS within 2 months

12. Criterion modified per Amendment 1

    12.1 Have screening laboratory test results within the following parameters, if 1 or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:

a. Hemoglobin	≥9 g/dL	SI: ≥90 mmol/L
b. White blood cells	≥3.0 × 10^3/µL	SI: ≥3.0 GI/L
c. Neutrophils	≥1.5 × 10^3/µL	SI: ≥1.5 GI/L
d. Platelets	≥100 × 10^3/µL	SI: ≥100 GI/L
e. Serum creatinine	≤1.8 mg/dL	SI: ≤159 µmol/L
f. Aspartate aminotransferase (AST)	≤2 × ULN	
g. Alanine aminotransferase (ALT)	≤2 × ULN	

Concomitant or previous medical therapies received

13. Regular treatment with the following agents with no changes in dose or frequency is permitted as follows:

    a) Oral glucocorticoids (average daily dose ≤10 mg of prednisolone or equivalent) for ≥6 weeks and at a stable dose ≥2 weeks prior to first dose of study intervention.

    If currently not using oral glucocorticoids, must not have received them for ≥6 weeks prior to the first dose of study intervention.

    b) Nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesics at a stable dose ≥2 weeks prior to first dose of study intervention.

    c) Endothelin receptor antagonists (eg, bosentan, ambrisentan and macitentan) at a stable dose ≥2 weeks prior to first dose of study intervention.

d) Phosphodiesterase 5 inhibitors (eg, sildenafil and tadalafil) for at a stable dose ≥2 weeks prior to first dose of study intervention.

e) Prostacyclins (eg, epoprostenol, iloprost and treprostinil) for at a stable dose ≥2 weeks prior to first dose of study intervention.

f) Permitted topical medications for cutaneous disease for ≥4 weeks prior to first dose of study intervention.

Tuberculosis

14. Are considered eligible according to the following TB screening criteria:

a) Have no history of latent or active TB before screening. An exception is made for participants who have a history of latent TB and satisfy 1 of the following criteria:

are currently receiving treatment for latent TB,

OR

will initiate treatment for latent TB before the first administration of study intervention,

OR

have documentation of having completed appropriate treatment for latent TB within 5 years before the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation. Patients with a history and documentation of having completed appropriate treatment for latent TB more than 5 years before the first dose of study intervention are not eligible.

b) Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

c) Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first administration of study intervention.

d) Within 2 months before the first administration of study intervention, have a negative interferon gamma release assays (IGRAs; QuantiFERON-TB® or T-SPOT®) result, or have a newly identified positive IGRA result (see Laboratory Manual) in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study intervention.

A subject whose first IGRA result is indeterminate should have the test repeated. If the second IGRA test result is also indeterminate, the subject may be enrolled without treatment for latent TB, if active TB is ruled out, their chest radiograph

shows no abnormality suggestive of TB (active or old, inactive TB), and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

NOTE: IGRA is not required at screening for participants with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; participants with documentation of having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

e) Have a chest radiograph (both posterior-anterior and lateral views) taken ≤12 weeks before the first administration of study intervention and read by a qualified physician to read radiogram (eg, a radiologist or pulmonologist), with no evidence of current, active TB or old, inactive TB. Chest computerized tomography (CT) may also be performed if deemed appropriate by the investigator.

Sex and Contraceptive/Barrier Requirements

15. A woman of childbearing potential must have a negative urine pregnancy test result at screening and baseline.

16. A woman must be (as defined in Section 10.5, Appendix 5: Contraceptive and Barrier Guidance)

    a. Not of childbearing potential

    b. Of childbearing potential and

        - Practicing a highly effective, preferably user-independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5: Contraceptive and Barrier Guidance.

    Note: If a participant's childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin using a highly effective method of contraception, as described throughout the inclusion and exclusion criteria.

17. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 12 weeks after the last administration of study intervention.

18. Criterion modified per Amendment 1

    18.1 Male participants must agree to the following during the study and for at least 12 weeks after the last dose of study intervention:

    - Must agree not to donate sperm for the purpose of reproduction.
    - A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person.
    - Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

Informed Consent

19. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

20. Must sign a separate informed consent if he or she agrees to provide an optional DNA sample for research. Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study.

21. Willing and able to adhere to the lifestyle restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Medical Conditions

1. History of liver or renal insufficiency (estimated creatinine clearance below 60 mL/min); significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances.

2. Has any known severe or uncontrolled SSc complications including hemoptysis, pulmonary hemorrhage, renal crisis.

3. Has severe pulmonary hypertension as determined by echocardiogram and pulmonary function test or right heart catheterization. Severe pulmonary hypertension includes but not limited to;

- Left ventricular ejection fraction <40%
- Peak tricuspid regurgitation velocity (m/s) >3.4
- Resting heart rate <50 bpm
- Systolic blood pressure < 90 mm Hg
- ECG findings suggestive of significant conduction abnormalities

4. Has an interstitial lung disease requiring oxygen therapy.

5. Has any rheumatic disease other than SSc such as RA, polymyalgia rheumatica (PMR), systemic lupus erythematosus, polymyositis/dermatomyositis that could interfere with assessment of SSc.

6. Has a current diagnosis or signs or symptoms of severe, progressive, or uncontrolled renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances. (or, in the investigator's opinion, any other concomitant medical condition that places the participant at risk by participating in this study).

7. Has or has had any major ischemic event, within 12 weeks of first study intervention.

8. Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.

9. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (eg, mucocutaneous candidiasis, but excluding fungal infections of the nail beds), or open, draining, or infected skin wounds or ulcers.

10. Has or has had a serious infection (eg, sepsis, pneumonia, or pyelonephritis), or has been hospitalized or received IV antibiotics for an infection during the 2 months before first study intervention.

11. Has or has had a nontuberculous mycobacterial infection or clinically significant opportunistic infection (eg, cytomegalovirus, pneumocystosis, invasive aspergillosis).

12. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to inclusion criterion 14 for information regarding eligibility with a history of latent TB.

13. Has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis within 6 months of first study intervention, if that prosthesis has not been removed or replaced.

14. Has a history of or is infected with human immunodeficiency virus (HIV [positive serology for HIV antibody]); tests positive for hepatitis B virus (HBV) infection; has antibodies to hepatitis C virus (HCV) at screening.

15. During the 6 weeks prior to baseline, have had any of (a) confirmed SARS-CoV-2 infection (test positive) (coronavirus disease 2019 [COVID-19]), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection.

    An exception to this criterion maybe granted if a participant has a documented negative result for a validated SARS-CoV-2 test:

    (i) Obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

    AND

    (ii) With absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit.

    NOTES on COVID-related exclusion:

    - The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.
    - Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

16. Has experienced a recent single dermatomal herpes zoster eruption within the past 4 months. Has ever had multi-dermatomal herpes zoster (defined as appearance of lesion outside the primary or adjacent dermatome) or central nervous system zoster infection.

17. Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a non-melanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months before the first study intervention administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study intervention).

    Note: premalignant lesions should be discussed with the sponsor medical monitor.

18. Has a transplanted organ including HSCT (with exception of a corneal transplant >3 months before the first study intervention).

19. Has known allergies, hypersensitivity, or intolerance to guselkumab or its excipients.

Diagnostic Assessments

20. Has had major surgery (eg, requiring general anesthesia and hospitalization) within 8 weeks before screening, or has not fully recovered from such surgery, or has such surgery planned during the time the participant is expected to participate in the study.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

21. Has a history of drug or alcohol abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, within 1 year before screening.

Prior/Concomitant Therapy

22. Has previously been treated with any investigational or approved immune-modulatory biologic agent prior to first study intervention, including but not limited to:

    - Has received therapy:

      IL-23 inhibitor therapy (including but not limited to guselkumab, risankizumab, tildrakizumab, brazikumab, mirikizumab)

      IL-12/23 inhibitors (ustekinumab)

      IL-17 inhibitors (secukinumab, ixekizumab, brodalumab)

    - Has received therapy within 12 weeks, or 5 half-lives (whichever is longer):

      Tocilizumab (Actemra)

      Sirukumab, sarilumab, mavrilimumab, abatacept, belimumab

      Tyrosine kinase inhibitor (nintedanib)

      Systemic and topical Janus kinase inhibitor (eg, tofacitinib, upadacitinib)

    - Has received therapy within 1 year, or 5 half-lives (whichever is longer):

      Rituximab

    Note: Not listed biologic agents should be discussed and agreed with the sponsor medical monitor.

23. Has been treated with:

    - Within 6 months of study intervention:

Any cytotoxic agents (cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents)

Intravenous immunoglobulin (IVIG), apheresis therapy (plasmapheresis or leukopheresis)

- Within 6 weeks of first study intervention:

  Systemic immunosuppressive agents (including but not limited to cyclosporine A, azathioprine, tacrolimus, sirolimus, sulfasalazine, leflunomide with cholestyramine washout or mycophenolate mofetil/mycophenolic acid)

  Intramuscular, intra-articular, intrabursal, epidural, intra-lesional or IV glucocorticoids

Any questions or concerns with the use of these therapies should be discussed with the study sponsor and/or medical monitor.

Prior/Concurrent Clinical Study Experience

24. Received an investigational intervention (including investigational vaccines) within 3 months or 5 half-lives (whichever is longer) or used an invasive investigational medical device within 3 months before the planned first dose of study intervention or is currently enrolled in an investigational study.

25. Bacille Calmette-Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks of randomization.

26. Is a woman who is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 12 weeks after the last administration of study intervention.

27. Is a man who plans to father a child while enrolled in this study or within 12 weeks after the last administration of study intervention.

28. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Other Exclusions

29. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded

from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.

5.5. Criteria for Temporary Delaying Enrollment/Randomization/Administration of Study Intervention Administration

This section is not applicable for this study.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Participants will be randomly assigned in a 1:1 ratio to 1 of the following study intervention groups:

- Guselkumab (Group/Arm A): Guselkumab 400 mg IV administration Weeks 0, 4, and 8 (induction) followed by guselkumab 200 mg SC administration Q4W from Week 12 until Week 48 (maintenance).
- Placebo (Group/Arm B): Matching placebo IV administration Weeks 0, 4, and 8 (induction) followed by matching placebo SC administration Q4W from Week 12 until Week 48 (maintenance).

Intravenous study intervention (including the flush) should be administered over a period of not less than 1 hour, and not more than 2 hours. The infusion (including the flush) should be completed within 6 hours of preparation.

Since 2 SC injections by using 100 mg/mL prefilled syringe (PFS) are administered at visits, each injection of study intervention should be given at a different location of the body.

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Guselkumab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

During the LTE, participants will receive guselkumab treatment in LTE as below depending on the arms they were in the main study:

- Group/Arm A (guselkumab arm from the main study) : Guselkumab 200 mg SC and placebo IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100.

- Group/Arm B (placebo arm from the main study): Placebo SC and guselkumab 400 mg IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100.

After Week 68 participants who have been appropriately trained in the self-administration of study intervention may self-administer study intervention. At-home administration is allowed for selected visits. More details are provided in Section 4.1.2 Self-Administration of Study Intervention.

6.1.1. Combination Products

For this protocol, the term combination product refers to the single integral drug-device combination.

The sponsor-manufactured combination product for use in this study is the prefilled syringe (PFS) assembled with an UltraSafe Plus™ Passive Needle Guard (PFS-U). Additional details on the PFS-U are provided in Section 6.2.

All combination product deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) shall be documented and reported

by the investigator throughout the study. These deficiencies will be reported as product quality complaints (PQC) (see Section 10.4.6, Product Quality Complaint Handling) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

For IV administrations, guselkumab final vialed product (FVP [IV]) is supplied as a sterile solution in a single-use glass vial containing 20 mL at a concentration of 10 mg/mL. Study intervention will be prepared for IV administration based on the instructions provided to clinical sites in the IPPI.

For SC administrations, guselkumab will be supplied as a 100 mg/mL sterile solution in a single-use PFS assembled in an UltraSafe Plus™ Passive Needle Guard (PFS-U). For SC administration, placebo for guselkumab will be supplied as a 1 mL sterile solution in a single-use PFS assembled in a PFS-U.

Guselkumab and placebo for guselkumab should be clear and colorless to light yellow solution that may contain small translucent particles. Do not use guselkumab or placebo for guselkumab if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material, but avoid direct exposure to sunlight. Aseptic technique must be used during the preparation and administration of the study intervention material.

Study personnel will instruct participants on how to transport, store, and administer study intervention for at-home use during the LTE as indicated for this protocol.

Refer to the Investigational Product Procedures Manual (IPPM) and Investigational Product Procedure Instructions (IPPI) for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials containing hazardous liquids, such as needles and syringes should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the IPPI.

Participants who will be self-administering study intervention at home will receive detailed instructions for study intervention storage and disposal of used syringes and handling of unused study material. These participants will receive a sharps container to dispose of used syringed and will be instructed to return the sharps container and/or unused cartons with syringes. Participants who self-administer at home will record study intervention administrations with time and date information on a diary card.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by presence of ILD (yes, no), baseline mRSS (low [≥10 to ≤15] or high [≥16 to ≤22]), and baseline anti-topoisomerase I antibody status (positive, negative). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

To maintain the study blind, the study intervention container will have a label containing the study name, study intervention number, and reference number. A tear-off label is designed to be torn off, separated from the study intervention container, and attached to the participant's source documents. The label will not identify the study intervention in the container. However, if it is necessary for a participant's safety, the study blind may be broken and the identity of the study intervention ascertained. The study intervention number will be entered in the eCRF when the study

intervention is administered. The study interventions will be identical in appearance and will be packaged in identical containers.]

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, study intervention serum concentrations, anti-guselkumab antibodies, study intervention preparation/accountability data, intervention allocation, and biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock (DBL) and unblinding.

All sponsor personnel, site personnel and participants will remain blinded to the treatment assignments until the Week 52 DBL.

The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

6.4. Study Intervention Compliance

Study intervention will be administered at site as an IV infusion or SC injection by qualified staff. The details of each administration will be recorded in the eCRF. For IV infusions, this will include date and start and stop times of the IV infusion and volume infused; for SC injections, this will include date and time of SC injection.

Study site personnel will maintain a log of all study intervention administered. Study intervention supplies for each participant will be inventoried and accounted for.

6.5. Dose Modification

No treatment/dose adjustment of study intervention will be permitted throughout the study period.

6.6. Continued Access to Study Intervention After the End of the Study

This protocol is designed to provide participants with up to approximately 104 weeks of treatment, including LTE.

No continued access is proposed for this study as this is a PoC study. At the end of their participation in the study, the participants will be instructed that they should return to their primary physician to determine standard of care, if applicable.

6.7. Treatment of Overdose

For this study, any dose of guselkumab greater than the highest dose at a single visit specified in this protocol will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until guselkumab can no longer be detected systemically.
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8. Concomitant Therapy

Prestudy therapies including specific SSc therapies administered up to 60 days before first dose of study intervention must be recorded at screening.

Concomitant therapies including specific SSc therapies must be recorded throughout the study beginning with start of the screening to the final safety follow-up visit. Concomitant therapies should also be recorded beyond the final safety follow-up visit only in conjunction with SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study. Any questions or concerns with the use of concomitant therapies should be discussed with the study sponsor and/or medical monitor.

NSAIDs or Other Analgesics

Participants may be treated with NSAIDs, including COX-2 inhibitors, during the study. The participant's standing dose should remain stable during the study, unless dose reduction is required for safety reasons. The choice and doses of NSAIDs are at the discretion of the investigator. For participants who receive corticosteroids and/or NSAIDs, prophylactic treatment such as rebamipide, or H2-receptor blockers should be considered. Prophylactic treatment should be added according to the investigator's discretion.

Oral Corticosteroids

Participants may receive corticosteroids at a stable dose of ≤10 mg/day of prednisolone or equivalent during the study. Increases in corticosteroid doses for treatment of SSc are not allowed during the study. To treat non-SSc-related conditions such as asthma, increased doses of oral corticosteroids of up to 20 mg of prednisone daily (or equivalent) for 2 weeks are permitted. The dose of the corticosteroid should be tapered down to the previous level as rapidly as medically possible.

Medications for Pulmonary Arterial Hypertension

Participants may be treated with following medications for pulmonary arterial hypertension: endothelin receptor antagonists (eg, bosentan, ambrisentan and macitentan), phosphodiesterase 5 inhibitors (eg, sildenafil and tadalafil), and prostacyclins (eg, epoprostenol, iloprost and treprostinil). The dose should remain stable during the study.

ACE Inhibitors, Calcium-Channel Blockers, or Protein-Pump Inhibitors

Participants receiving ACE inhibitors, calcium-channel blockers, proton-pump inhibitors, and/or oral vasodilators have to be on a stable dose during the study, unless dose adjustments are required for safety reasons.

Prohibited and restricted therapies

- During the study

  IL-23 inhibitor therapy (including but not limited to guselkumab, risankizumab, tildrakizumab, brazikumab, mirikizumab)

  tocilizumab

  sirukumab, sarilumab, mavrilimumab, abatacept, belimumab

  IL-12/23 inhibitors (ustekinumab)

  IL-17 inhibitors (secukinumab, ixekizumab, brodalumab)

  tyrosine kinase inhibitor (nintedanib)

  Any live viral or live bacterial vaccination

  Rituximab

  Any cytotoxic agents (cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents)

Intravenous immunoglobulin (IVIG), apheresis therapy (plasmapheresis or leukopheresis)

Systemic immunosuppressive agents (including but not limited to cyclosporine A, azathioprine, tacrolimus, sirolimus, methotrexate, sulfasalazine, leflunomide with cholestyramine washout or mycophenolate mofetil/mycophenolic acid)

Intramuscular, intra-articular, intrabursal, epidural, intra-lesional or IV GCs

Pirfenidone

Systemic and topical Janus kinase inhibitors (eg, tofacitinib, upadacitinib)

Other biologics

Any investigational agents/treatments

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Rescue Medication

In the event that a participant experiences worsening criteria (Criteria: increase from baseline ≥5 in mRSS), investigators will have the option to treat with protocol-allowed rescue therapy after Week 24.

Oral Corticosteroid ≤20 mg/day of prednisolone or equivalent

Immunomodulator (Azathioprine), within the approved dose for SSc

If rescue therapy as stipulated above fails to control SSc symptoms sufficiently, the investigator should consider discontinuing the patient from the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The investigator or sponsor believes that there are no further benefit of continuing the study for the participants.
- The participant becomes pregnant or planning to become pregnant while enrolled in this study or within 12 weeks after the last administration of study intervention.
- Noncompliance with study intervention administration.
- The participant initiates treatment with prohibited therapies listed in Section 6.8 unless agreed upon with the sponsor medical monitor.

- The participant is deemed ineligible according to the following TB screening criteria:

  A diagnosis of active TB is made.

  A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.

  A participant undergoing evaluation has a chest radiograph or chest CT with evidence of current active TB and/or a positive QuantiFERON-TB test or T-SPOT test result, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next study intervention administration and continued to completion (see also Section 8.2.9). Indeterminate QuantiFERON-TB test or borderline T-SPOT results should be handled as in Section 8.2.9. Participants with persistently indeterminate QuantiFERON-TB test results or borderline T-SPOT may continue without treatment for latent TB if active TB is ruled out, their chest radiograph or chest CT shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor and recorded in the participant's source documents and initialed by the investigator.

  A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The participant has a serious adverse reaction that is related to an injection or an infusion, including an injection-site or infusion reaction, resulting in bronchospasm with wheezing and/or dyspnea that requires ventilatory support OR that results in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg.

- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

- The participant has severe liver test abnormalities that are not transient and are not explained by other etiologies. Such abnormalities would include (see Section 10.6, Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments):

  Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5 × ULN.

  ALT or AST ≥3 × ULN for more than 4 weeks.

  ALT or AST ≥3 × ULN and cannot be monitored weekly for 4 weeks.

  ALT or AST ≥3 × ULN and TBL ≥2 × ULN or international normalized ratio [INR] >1.5 (INR not acceptable for participants on anticoagulants).

  ALT or AST ≥3× ULN and symptoms (new or worsening) believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

- The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allowing participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study intervention.

Discontinuation of a participant's study intervention must be strongly considered under the following conditions:

- The participant develops a serious infection, including but not limited to sepsis or pneumonia.
- The participant develops a severe injection-site or infusion reaction.

If a participant discontinues study intervention for any reason before the end of the double-blind phase, then the assessments should be obtained as specified in the SoA (Section 1.3). Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets 1 of the conditions outlined in Section 10.6, Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments, or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion) as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research sample:

- The collected sample will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research sample, in which case the sample will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the sample has been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research sample will be destroyed. The sample destruction process will proceed as described above.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: ECG and vital signs (blood pressure, pulse rate, respiratory rate, and axillary body temperature) should be performed first, and then blood draws for PK or laboratory measurements. Urine and blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

For each participant, the maximum amount of blood drawn in this study will not exceed 567 mL through Week 112.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 3: Volume of Blood to be Collected from Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post-intervention assessments)			
- T-spot	10	1	10
- Hematology	2 - 3	26	52 - 78
- Serum chemistry	2.5	26	65
- Serology (HIV, HBV, HCV)	8.5	1	8.5
- HBV DNA testing	6	8	48
Pharmacokinetic/Immunogenicity samples	7.5	25	187.5
Pharmacodynamic/Biomarker samples			
- PBMCs	2 × 8	4	64
- Serum biomarkers	8.5	7	59.5
Autoantibodies	3	1	3
Pharmacogenomic sample[b]			
- EDTA	4 - 6	1	4 - 6
- Paxgene tube	5	3	15
Approximate Total[c]			516.5 – 544.5

Abbreviations: DNA=deoxyribonucleic acid; EDTA= ethylenediaminetetraacetic acid; HBV= hepatitis B virus; HCV= hepatitis C virus; HIV= human immunodeficiency virus; PBMC= peripheral blood mononuclear cells

a. Calculated as number of samples multiplied by amount of blood per sample.
b. A blood sample will be collected only from participants who have consented to provide an optional DNA and RNA samples for research.
c. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Screening

At the screening visit, written informed consent must be obtained from the participant for this program by the principal investigator or designee before performing any protocol-specific procedure. Procedures to be performed at the screening visit are outlined in the SoA (Section 1.3).

Women of childbearing potential must have a negative urine pregnancy test result at screening. Participants must be reminded that they are required to use a highly effective method of contraception during the study (as described in Inclusion Criteria [Section 5.1]) and must continue taking such precautions for 12 weeks after receiving the last administration of study intervention. The method(s) of contraception used by each participant must be documented.

Participants must undergo testing for TB (Section 8.2.9) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph or chest CT results.

Participants with a negative QuantiFERON-TB test or T-SPOT result are eligible to continue with registration procedures.

Participants with a newly identified positive QuantiFERON-TB or T-SPOT test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised participants.

A participant whose first QuantiFERON-TB test result is indeterminate or T-SPOT test result is borderline should have the test repeated. If the second QuantiFERON-TB or T-SPOT test result is also indeterminate or borderline, the participant may be enrolled without treatment for latent TB if his/her chest radiograph or chest CT shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator and Sponsor.

An assessment of all screening laboratory test results, clinical data, and concomitant medication data will be made by the principal investigator or designee to confirm that the participant satisfies all inclusion criteria and does not violate any exclusion criteria.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the Schedule of Activities (Section 1.3) for the timing and frequency of all sample collections.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB)
- IPPM and IPPI
- Instruction for use of prefilled syringe for site staff
- Instruction for use of prefilled syringe for subjects
- Training guide for investigators for use of prefilled syringe
- Subject diary for at home administration / self-administration
- Laboratory manual
- eCRF completion instructions
- Participant recruitment materials (if needed)
- Sample ICF
- PRO questionnaire and PRO completion guidelines
- IWRS manual
- CT image acquisition procedure manual and CT technologist instruction form
- Biopsy manual
- Capillaroscopy manual and quick reference guide
- Pulmonary function test manual

8.1. Efficacy Assessments

Efficacy assessments will include the following:

- mRSS
- ACR CRISS score
- Pulmonary function tests (PFTs):
  - FVC and % of predicted FVC
  - DLCO (ml/min/mm Hg) and % of predicted DLCO (hemoglobin-corrected)
- PhGA
- Patient-Reported Outcomes (PROs):
  - PGA
  - Health Assessment Questionnaire-Disability Index (HAQ-DI)
  - Frequency Scale for the Symptoms of Gastroesophageal reflux disease (FSSG) Questionnaire
- Digital ulcer assessment
- Nailfold Capillaroscopy
- Lung HRCT (centrally read)

8.1.1. Modified Rodnan Skin Score

The mRSS is a validated physical examination method for estimating skin induration. It correlates with biopsy measures of skin thickness and reflects prognosis and visceral involvement, especially in early disease. It is scored on 0 (normal) to 3 (severe induration) ordinal scales over 17 body areas, with a maximum score of 51 and is used to categorize severity of SSc (Khanna 2007). It has been extensively used as a primary and secondary outcome measure in randomized clinical trials (Khanna 2016a; Khanna 2020). This assessment should be performed by a physician who is experienced and trained in skin scoring. To prevent inter-observer variability, the same physician must perform skin scoring for the same participant throughout the entire study.

8.1.2. American College of Rheumatology Combined Response Index in Diffuse Cutaneous Systemic Sclerosis Score

ACR CRISS is composite response index for clinical trials in early dcSSc developed by an international group of experts in SSc. Application of ACR CRISS algorithm in a randomized clinical trial is a 2-step process. Firstly, evaluate if participants have met the criterion for not-improved. If yes, these participants are assigned a probability score of 0.0.

Investigators will evaluate if the participants have met the criterion:

- New scleroderma renal crisis
- Decline in FVC % predicted ≥15% (relative), confirmed by another FVC test within a month, HRCT to confirm ILD (if previous HRCT of chest did not show ILD) and FVC <80% of predicted*
- New onset of left ventricular failure (defined as left ventricular ejection fraction ≤45%) requiring treatment*
- New onset of PAH on right-sided heart catheterization requiring treatment*

* Attributable to systemic sclerosis

For the remaining participants, calculate the probability based on change in 5 measures: mRSS, % of predicted FVC, HAQ-DI, patient's global assessment, and physician's global assessment, where each measure has a probability score between 0 and 1 (Khanna 2016b). ACR CRISS sore will be calculated by the sponsor.

8.1.3. Pulmonary Function Tests

The following lung function measurements will be performed locally:

- FVC and % of predicted FVC
- DLCO (ml/min/mm Hg) and % of predicted DLCO (hemoglobin-corrected)

Also, oxygen saturation data will be collected.

8.1.4. Physician Global Assessment

PhGA rated subject's overall SSc condition will be assessed, using a 10 cm visual analogue scale where 0 excellent and 10 extremely poor.

8.1.5. Patient-reported Outcomes

The participant's overall health and physical function would be assessed using 2 PRO instruments: PGA and HAQ-DI. In addition, the esophageal symptoms of gastroesophageal reflux disease (GERD) will be evaluated using the Frequency Scale for the Symptoms of GERD (FSSG) questionnaire.

Patient Global Assessment

Participant's overall health will be assessed using the patient-reported outcome instrument of PGA. The PGA would rate subject's overall health related to SSc in the past 7 days, using a 10 cm visual analogue scale where 0 excellent and 10 extremely poor.

Health Assessment Questionnaire -Disability Index

The Stanford HAQ is a brief self-report questionnaire assessing physical function pertaining to activities of daily living across 8 domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Originally developed for use in RA, it has been successfully applied to a variety of rheumatic conditions, including idiopathic inflammatory myopathy. The Stanford HAQ translated into Japanese with culturally appropriate modifications of the arising, eating, and reach category questions will be used in the study (Matsuda 2003).

Frequency Scale for the Symptoms of Gastroesophageal reflux disease (FSSG)

The FSSG questionnaire is a succinct questionnaire to evaluate esophageal symptoms of GERD which is validated based on endoscopic esophagitis. The original version of FSSG consists of the most prevalent 7 acid-reflux related and 5 dysmotility-related symptoms of GERD with higher scores being more indicative of underlying GERD. Each score was determined as follows: 0 never, 1 occasionally, 2 sometimes, 3 often, and 4 always.

The PRO instruments will be provided in the local language in accordance with local guidelines.

- The PRO instruments must be available for regulators and for Institutional Review Board (IRB)/Independent Ethics Committee (IEC) submissions, therefore the PRO instruments or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol.
- The PRO and AE data will not be reconciled with one another.

8.1.6. Digital Ulcer Assessments

Digital ulcers are defined as a full thickness (>3mm in maximal diameter) skin lesion with loss of epithelium including lesions covered by eschar (Note: Pitting scars and hyperkeratotic lesions are excluded). Healing is defined by re-epithelialization with loss of pain and exudate. The digital ulcer assessments would be performed by the investigator designee during the study as specified in the SoA (Section 1.3). Ulcer counts and ulcer burden would be calculated by the sponsor.

8.1.7. Nailfold Capillaroscopy

Nailfold capillaroscopy is a non-invasive method to visualize the nailfold capillaries and assess microvascular morphology. Nailfold capillary abnormalities are included in ACR/EULAR classification criteria for SSc. Nailfold capillary abnormalities are evaluated by using nailfold capillaroscopy. The typical changes of the nailfold capillaries during SSc include the total number of capillaries, capillary dimension, capillary morphology, hemorrhages, blood flow velocity in capillaries, and length of nailfold. These changes would be calculated (Smith 2020; Smith 2010; Smith 2012). Visual media will be taken. For details, refer to the manual.

8.1.8. High-resolution Computed Tomography (HRCT) Assessment

Lung involvement is one of the most important cause of morbidity and mortality in patients with SSc. Because of recent advancement of computer-based scoring, analysis of CT images is drawing attention as a method to assess fibrotic changes in ILD. Texture-based analysis and computer vision-based approaches can be applied to imaging data, and used to evaluate the extent of lung fibrosis in chest CT images (Weatherley 2019). This assessment should be done at central. For details on HRCT, refer to CT technologist instruction form.

8.2. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.2.1. Physical Examinations

Physical examinations will be performed as specified in the Schedule of Activities (Section 1.3). While assessment of the participants for safety and efficacy requires some physical examination by an investigator at all visits, a more complete, detailed physical exam will be performed at specified visits.

Height and weight of the participants will be measured at specified visits. Participants will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

8.2.2. Vital Signs

Temperature (axillary), pulse/heart rate, respiratory rate, blood pressure will be assessed.

Through Week 112, vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained before and approximately every 30 minutes during every IV infusion, and for 1 hour at approximately 30-minute intervals after completion of the final IV infusion. Vital signs should be obtained before and approximately 30 minutes after the final SC injection.

8.2.3. Electrocardiograms

A 12-lead ECG will be performed at screening and at timepoints specified in the SoA (Section 1.3).

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2: Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

8.2.5. Interstitial Lung Disease Monitoring

The presence of ILD must be evaluated at screening using chest x-ray/lung HRCT and/or PFTs (FVC and DLCO). All participants must be monitored with lung HRCT, and/or PFTs (FVC and DLCO) as scheduled in Section 1.3 during the study.

8.2.6. Adverse Events Temporally Associated with Infusion

Any AE (except laboratory abnormalities) that occurs during or within 1 hour after the IV infusion of study intervention will be carefully evaluated. Minor infusion-related AEs may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study intervention is stopped because of an AE that, in the opinion of the investigator, is not severe or does not result in a SAE, the infusion may be restarted with caution.

8.2.7. Injection-site Reactions

An injection-site reaction is any adverse reaction at a SC study intervention injection site. Injection sites will be evaluated for reactions and any injection-site reaction will be recorded as an AE.

8.2.8. Hypersensitivity Reactions

Before any SC injection or IV infusion, appropriately trained personnel and medications must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be observed carefully for symptoms of a hypersensitivity reaction (eg, urticaria, itching, hives). If a

mild or moderate hypersensitivity reaction is observed, acetaminophen, nonsteroidal anti-inflammatory drugs, and/or diphenhydramine may be administered.

In the case of a severe hypersensitivity reaction (eg, anaphylaxis), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available at the study site where the injections or infusions are being administered.

Participants who experience serious adverse reactions related to an injection or infusion should be discontinued from further study intervention administrations.

Participants who experience reactions following an injection or infusion that result in bronchospasm with wheezing and/or dyspnea that requires ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mm Hg will not be permitted to receive additional study intervention.

Participants who experience reactions suggestive of serum sickness-like reactions (resulting in symptoms such as myalgia and/or arthralgia with fever and/or rash that are not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study intervention, should be discontinued from further study intervention administrations. Note that these symptoms may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

8.2.9. Tuberculosis evaluations

8.2.9.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph and/or CT results. If either the QuantiFERON-TB test or T-SPOT is positive, the participant is considered to have latent TB infection for the purposes of eligibility for this study.

Participants with a negative QuantiFERON-TB (or T-SPOT if performed) test result are eligible to continue with screening procedures. Participants with a newly identified positive QuantiFERON-TB (or T-SPOT if performed) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. Otherwise, the participant will be excluded from the study.

A participant whose first QuantiFERON-TB test result is indeterminate or T-SPOT test result is borderline should have the test repeated. In the event that the second QuantiFERON-TB test or T-SPOT result is also indeterminate or borderline, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the Sponsor and recorded in the participant's source documents and initialed by the investigator.

8.2.9.2. Ongoing Tuberculosis Evaluation

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:

  Persistent fever?

  Unintentional weight loss?

  Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON-TB or T-SPOT test, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment for latent TB is warranted.

Study intervention administration should be interrupted during the investigation. A positive QuantiFERON-TB test or T-SPOT test result should be considered detection of latent TB. If the QuantiFERON-TB test result is indeterminate or T-SPOT result is borderline, the test should be repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study intervention and be encouraged to return for all subsequent scheduled study visits according to the SoA (Section 1.3).

8.2.10. Infections

Study intervention administration should not be given to a participant with a clinically important, active infection. Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits. If a participant develops a serious infection, including but not limited

to sepsis or pneumonia, discontinuation of study intervention (ie, no further study intervention administrations) must be considered.

8.2.11. Hepatitis B Monitoring

For participants who are eligible with surface antigen (HbsAg) negative, core antibody (anti HBc) and/or surface antibody (anti-HBs) positive, and HBV deoxy ribonucleic acid (DNA) test is negative, HBV DNA quantitation should be monitored at least every 3 months or shorter.

8.2.12. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQC, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For study intervention that meets the definition of a combination product, malfunctions or deficiencies of a device constituent will be reported as PQC.

Further details on AEs, SAEs, and PQC can be found in Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. Possible Hy's law case (AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN or INR > 1.5) is considered an important medical event and must be reported to the sponsor in an expedited manner using the Serious Adverse Event Form, even before all other possible causes of liver injury have been excluded. (INR criterion is not applicable to participants receiving anticoagulants.)

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

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

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For individual SAEs, the sponsor will make a determination of relatedness in addition to and independent of the investigator's assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious event, they will submit a safety report in narrative format to the investigators (and the head of the institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Adverse Events of Special Interest (AESI)

Any newly identified malignancy or case of active TB or ILD occurring after the first study intervention administration(s) in participants participating in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event for SAEs. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Pharmacokinetics

Serum samples will be used to evaluate the PK of guselkumab according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsors designee. Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Additional blood sampling may be considered when participant experienced SAE. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

At visits where only serum concentration of guselkumab will be evaluated (ie, no antibodies to guselkumab will be evaluated), 1 venous blood sample of sufficient volume should be collected, and each serum sample should be divided into 2 aliquots (1 for serum concentration of guselkumab, and a back-up). At visits where serum concentration of guselkumab and antibodies to guselkumab will be evaluated, 1 venous blood sample of sufficient volume should be collected, and each serum sample will be divided into 3 aliquots (1 each for serum concentration of guselkumab, antibodies to guselkumab, and a back-up).

8.4.2. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of guselkumab using a validated, specific, and sensitive method by or under the supervision of the sponsor's representative.

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

Based on the individual serum concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of guselkumab may be derived using population PK modeling. Details will be given in a population PK analysis plan.

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between serum concentrations of guselkumab and the efficacy measures and/or relevant PD endpoints, including biomarkers in blood or in skin biopsies, may be explored. Details will be given in a population PK/PD analysis plan if explored.

8.5. Pharmacogenomics

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary. Participant participation in pharmacogenomic research is optional.

8.6. Biomarkers

An optional biomarker sub-study will obtain a biopsy sample of non-lesional (unaffected) skin sample at Week 0, and lesional (at Week 0) skin at Week 0 and 24 from all participants who consent. For details, refer to the manual.

Data collected from these samples will be used for exploratory research that will include, but are not limited to, the following objectives:

- To understand the molecular effects of guselkumab.
- To understand SSc pathogenesis.
- To understand why individual participants may respond differently to guselkumab.
- To understand the impact of treatment with guselkumab on skin or systemic inflammation.
- To develop diagnostic tests to identify SSc or SSc populations that may be responsive or nonresponsive to treatment with guselkumab.

8.6.1. Pharmacodynamics

Peripheral blood mononuclear cell (PBMC) and serum samples will be collected at timepoints specified in the SoA (Section 1.3), to assess the blood cellular and molecular biomarkers to enable evaluation of target engagement in tissue/efficacy PD readouts.

8.7. Immunogenicity Assessments

Anti-guselkumab antibodies will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to guselkumab and the titer of confirmed positive samples will be reported as applicable. Serum samples positive for anti-guselkumab antibodies will be further characterized for Nabs to guselkumab. Other analyses may be performed to verify the stability of anti-guselkumab antibodies and/or further characterize the immunogenicity of guselkumab.

Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to guselkumab will be performed using a validated assay method by or under the supervision of the sponsor.

8.8. Autoantibodies

Samples will be collected at screening (see Section 1.3), to evaluate the presence of autoantibodies (including, but not limited to anti-RNA polymerase, anti-centromere, and anti-topoisomerase). Anti-centromere antibodies are very useful in distinguishing patients with SSc from healthy controls and from patients with other connective tissue disease. Anti-centromere antibodies often predict a limited skin involvement and the absence of pulmonary involvement anti-RNA-polymerase autoantibodies occur less frequently and are also predictive of diffuse skin involvement and systemic disease (Ho 2003).

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Hypotheses

This is a PoC study aimed at detecting an early efficacy signal of guselkumab in participants with SSc, compared to placebo, to support further clinical development.

- The null hypothesis is that the treatment difference between guselkumab and placebo for the primary endpoint is 0.
- The alternative hypothesis is that the treatment difference between guselkumab and placebo for the primary endpoint is ≠0.

Due to the PoC nature of this study, a 2-sided alpha of 0.2 is allocated for testing this PoC hypothesis. The PoC objective will be considered met if the calculated p-value for testing this PoC hypothesis is less than 0.2.

9.2. Sample Size Determination

There is lack of positive placebo-controlled trials in dcSSc.

Taking into account the following 4 Phase 2/3 placebo-controlled trials in SSc with mRSS results reported in the ClinicalTrials.gov registry, a reasonable estimate of the standard deviation (SD) to be used in the sample size calculation of this study has been taken as 8.0.

Standard deviations of mRSS in Referenced Phase 2/3 Placebo-controlled Trials in SSc

Trial	Treatment group		Placebo group	
	N	Estimated SD	N	Estimated SD
A Double-Blind, Randomised, Placebo-controlled Trial Evaluating Efficacy and Safety of Oral Nintedanib Treatment for at Least 52 Weeks in Patients With Systemic Sclerosis Associated Interstitial Lung Disease (SSc-ILD) (NCT02597933)	288	4.582	288	4.412
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy and Safety of Tocilizumab Versus Placebo in Patients With Systemic Sclerosis (NCT02453256)	104	8.169	106	8.142
A Phase 2/3, Multicenter, Randomized, Double-blind, Placebo-controlled Study To Assess The Efficacy And Safety Of Tocilizumab Versus Placebo In Patients With Systemic Sclerosis (NCT01532869)	43	8.266	41	8.933
A Phase 2 Study to Evaluate Subcutaneous Abatacept vs. Placebo in Diffuse Cutaneous Systemic Sclerosis- a Double-blind, Placebo-controlled, Randomized Controlled Trial (NCT02161406)	44	7.562	44	7.562

Khanna et al (2006) revealed that a 95% confidence interval (CI) of [-4.7, -1.7] in mRSS change from baseline to 6 months was considered a clinically meaningful change. The lower bound of this 95% CI, -4.7, has been taken as the expected treatment difference in the sample size calculation of this study, assuming guselkumab can achieve a clinically meaningful change in most of guselkumab-treated participants.

Assuming an SD of 8 points, an 80% power at a 2-sided significance level of 0.20, with a 1:1 randomization ratio, to detect a treatment effect of -4.7 points, a total of at least 54 participants will be required.

Allowing for up to 2 participants randomized but without post-baseline efficacy assessments, approximately 56 (28 each) randomized participants are planned. In order to evaluate the inter-observer and intra-observer variability of the mRSS to support Phase 3 planning, it is desirable for each center to randomize 3 participants at least.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants who were randomized in the study.
Full Analysis Set	All randomized participants who received at least 1 dose (complete or partial) of study intervention.

Population	Description
	Note: Efficacy and participant information analyses will be based on the randomized treatment groups, regardless of the treatment they actually received.
Safety	All randomized participants who received at least 1 dose (complete or partial) of study intervention. Note: Safety will be analyzed based on the treatment they receive, regardless of the treatment groups to which they are assigned.
PK	All participants who received at least 1 complete dose of guselkumab and have at least 1 observed post dose PK data.
Immunogenicity	All participants who received at least 1 dose of guselkumab and have at least 1 observed post dose immune response data.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to each DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

An interim analysis will be performed when all participants have completed the Week 52 visit or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit or discontinued earlier.

Simple descriptive summary statistics, such as n, mean, SD, median, inter quantile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

9.4.2. Primary Endpoint

For primary endpoint (Change from baseline in mRSS at Week 24), treatment comparison will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model. The MMRM model includes treatment group, baseline mRSS, stratification factors, visit, treatment group by visit interaction, and baseline mRSS by visit interaction as fixed effects. Treatment effects will be estimated based on least-square (LS) means of the differences. The p-values for the LS mean differences along with the 2-sided 80% CI will be presented.

Sensitivity and subgroup analyses for the primary endpoint will be performed, if appropriate. The details of these analyses and data handling rules will be specified in the SAP.

9.4.3. Secondary Endpoints

All secondary efficacy endpoints will be summarized over time by treatment group. Treatment comparisons will be performed using an MMRM model where there are repeated continuous measurements or a logistic model where there is a dichotomous response variable. No adjustments for multiple comparisons will be made for the secondary endpoints and all p-values will be considered nominal. The detailed methods of analysis and the data-handling rules will be provided in the SAP.

9.4.4. Exploratory Endpoints

The detailed methods of analysis and the data-handling rules for the exploratory endpoints will be provided in the SAP.

9.4.5. Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a preexisting condition that has worsened since baseline.

Adverse events, SAEs, related AEs, and AEs by severity will be summarized by treatment group. More specification of other AESIs such as ILD will be described in the SAP.

Summaries, listings, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

Clinical Laboratory Tests

The laboratory parameters and change from baseline in selected laboratory parameters (hematology and chemistry), and the number of participants with abnormal laboratory parameters (hematology and chemistry) based on National Cancer Institute Common-Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grading will be summarized by intervention group.

Electrocardiogram

Clinically relevant abnormalities will be evaluated by frequency tabulations.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.6. Other Analyses

Pharmacokinetic Analyses

Unless otherwise noted, PK analyses will be based on the PK Analysis Set. Detailed rules for the analysis including exclusion from the PK analyses will be specified in the SAP.

All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented in the clinical study report.

Descriptive statistics will be used to summarize guselkumab serum concentrations at each sampling time point.

If sufficient data are available, population PK analysis of serum concentration-time data of guselkumab will be performed using nonlinear mixed effects modeling. If the population PK analysis is conducted, details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

Biomarkers Analyses

Characterization of gene expression changes in the skin during treatment would be analyzed as determined by RNA-seq at Weeks 0 and 24. If feasible, a non-lesional (unaffected) skin sample will be collected at Week 0; lesional (at Week 0) samples to be collected at both Weeks 0 and 24. If feasible, characterization of the tissue immunopathological changes in the skin as determined by immunohistochemistry (IHC)/ immunofluorescence (IF)/ in situ hybridization (ISH), as well as histology analysis (eg, fibrosis) will be performed. Multiparameter protein profiling (eg, imagine CyTOF) may be considered.

Immunogenicity Analyses

The incidence of anti-guselkumab antibodies will be summarized for the immunogenicity analysis set.

A listing of participants who are positive for anti-guselkumab antibodies will be provided. The maximum titers of anti-guselkumab antibodies will be summarized for participants who are positive for anti-guselkumab antibodies.

The incidence of Nabs to guselkumab will be summarized for participants who are positive for anti-guselkumab antibodies and have samples evaluable for Nabs to guselkumab.

Pharmacodynamic Analyses

Serum will be collected from all subjects to assess PD markers associated with guselkumab as well as markers related to SSc. Measurements may include but are not limited to serum levels of IL-17A, IL-17F, IL-22, beta defensin-2 (BD-2), and SAA. The samples will be collected at Weeks 0, 4, 12, 16, 24, 28, and 48 and analyzed by immunoassays. Broader proteomic profiling (eg, via Olink method) for biomarker discovery may be performed. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Blood samples for the isolation of PBMCs will also be collected for subsequent immunophenotyping analyses by multiparameter flow cytometry or mass cytometry (CyTOF) analysis to measure immune cell populations before and during treatment. The samples will be collected at Weeks 0, 4, 24, and 48. Gene expression analysis may also be performed; this may include single cell RNA-seq profiling. Additionally, serum samples for isolation of PBMCs should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study

Results of pharmacodynamic/biomarker analyses will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum concentrations of guselkumab and the efficacy measures and/or relevant PD endpoints, including biomarkers in blood or in skin biopsies, may be explored graphically when appropriate. If any visual trend is observed, additional analysis may be conducted if deemed necessary.

Pharmacogenomic Analyses

Genetic analysis may help to identify population subgroups that respond differently to a drug. A single DNA sample at Week 0 as specified in the SoA (Section 1.3) will be used to explore genetic factors that may influence molecular effects, clinical efficacy, or tolerability of guselkumab and to identify genetic factors associated with SSc. A locus of interest is the *IL12RB1* gene; a reported SSc risk allele has been identified in this gene and there is potential association with expression of the gene product (encoding a receptor for IL-23). Analysis applied to DNA samples may focus on genotyping, using molecular arrays to scan polymorphisms across the genome. Participation in the DNA sampling is optional.

Results will be presented in a separate report.

Interim Analysis

An interim analysis will be performed when all participants have completed EOS of the main study. All sponsor personnel will be unblinded at the analyses for internal decision-making and/or interactions with health authorities.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

ACR	American College of Rheumatology
ACR CRISS	American College of Rheumatology Combined Response Index in diffuse cutaneous systemic sclerosis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
CD	Crohn's disease
CI	confidence interval
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CT	computed tomography
DBL	database lock
dcSSc	diffuse cutaneous systemic sclerosis
DLCO	diffusing capacity of the lung for carbon monoxide
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EULAR	European League Against Rheumatism
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
FSSG	Frequency Scale for the Symptoms of Gastroesophageal reflux disease
FVC	forced vital capacity
GCA	giant cell arteritis
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
HAQ-DI	Health Assessment Questionnaire-Disability Index
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HRCT	high resolution computed tomography
HS	hidradenitis suppurativa
HSCT	hematopoietic stem cell transplant
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGRA	interferon gamma release assays
INR	international normalized ratio
IL	interleukin
IPPI	Investigational Product Procedure Instructions
ILD	interstitial lung disease
IPPM	Investigational Product Procedures Manual
IRB	Institutional Review Board
IV	intravenous
IVIG	intravenous immunoglobulin
IWRS	interactive web response system
Q4W	every 4 weeks
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
lcSSc	limited cutaneous systemic sclerosis
LN	lupus nephritis
LTE	long-term extension

mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measure
mRSS	modified Rodnan skin score
NOAEL	no observed adverse event level
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PFS	prefilled syringe
PFS-U	UltraSafe Plus™ passive needle safety device
PFT	pulmonary function test
PGA	patient global assessment
PhGA	physician global assessment
PK	pharmacokinetic(s)
PQC	product quality complaint
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PsA	psoriatic arthritis
PsO	plaque psoriasis
Q4W	every 4 weeks
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAP	statistical analysis plan
SAE	serious adverse event
SSc	systemic sclerosis
SC	subcutaneous
SD	standard deviation
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
UC	ulcerative colitis
ULN	upper limit normal
US	United States

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation.
PRO	Reports directly from the participant without interpretation by clinician or anyone else

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities (Section 1.3) by the central laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory.	
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT) Total and Direct bilirubin	Alkaline phosphatase Creatine phosphokinase (CPK) Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Cholesterol Triglycerides Magnesium C-reactive protein
	Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 6, Liver Safety.	
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells White blood cells Epithelial cells Crystals Casts Bacteria
	If dipstick result is abnormal, microscopy will be used to measure sediment. In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory.	
Other Screening Tests	• Urine Pregnancy Testing for women of childbearing potential only • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • QuantiFERON-TB test or T-SPOT	

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Protocol Supplementary Information, which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials

- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Informed consent may be obtained remotely. Refer to the Monitoring Guideline.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant

agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research. After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

If the participant is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the participant is obtained.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of guselkumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the clinical study report has been issued will be reported in a separate report and will not require a revision of the clinical study report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for

filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.6. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.7. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and

alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.3.8. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.3.9. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be

respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.11. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.12. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, for time of last AE recording).

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention

- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study within 12 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study intervention or the comparator. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability,

safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Protocol Supplementary Information, which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly.

Examples of Contraceptives

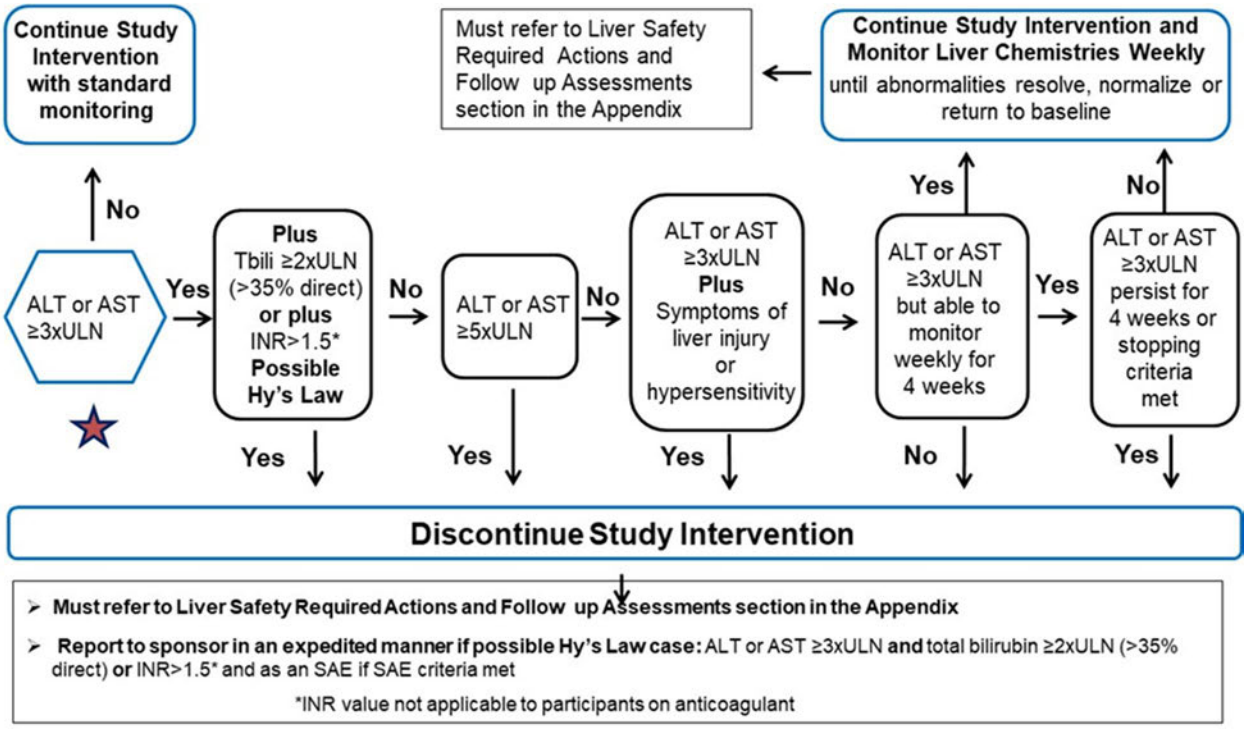
EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] oral
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male condom with or without spermicide
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

A. STOPPING ALGORITHM

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase, INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

B. FOLLOW-UP ASSESSMENTS

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT or AST-absolute	ALT or AST ≥5xULN
ALT or AST Increase	ALT or AST ≥3xULN persists for ≥4 weeks
Bilirubin[1,2]	ALT or AST ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin)
INR[2]	ALT or AST ≥3xULN **and** international normalized ratio (INR) >1.5
Cannot Monitor	ALT or AST≥3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT or AST ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring, and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study intervention • Report the event to the sponsor **within 24 hours** • Complete the liver event/expedited reporting form, and complete an SAE CRF if the event also met the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow-up Assessment column. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline **MONITORING:** **<u>If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:</u>** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A hepatology consultation is recommended **If ALT or AST≥3xULN AND total bilirubin <2xULN and INR ≤1.5:**	• Viral hepatitis serology[4] • Obtain blood sample for pharmacokinetic (PK) analysis approximately 60 minutes after the most recent dose[5] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), glutamate dehydrogenase (GLDH), and serum albumin • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event/expedited reporting form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF • Record alcohol use on the liver event alcohol intake form

• Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline • **Do not restart/rechallenge** participant with study intervention unless allowed per protocol and sponsor approval is granted	**If ALT or AST≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease; complete liver imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: In participants when serology raises the possibility of autoimmune hepatitis (AIH) In participants when suspected drug-induced liver injury (DILI) progresses or fails to resolve on withdrawal of study intervention In participants with acute or chronic atypical presentation • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT or AST ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT or AST ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin) or ALT or AST ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total). For participants who are eligible with negative HBsAg, and positive core antibody (anti-HBc) and/or surface antibody (anti-HBs), and negative HBV DNA test, HBV DNA quantitation should be monitored at least every 3 months or shorter.

5. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Investigational Product Procedures Manual (IPPM) and Investigational Product Procedure Instructions (IPPI).

10.7. Appendix 7: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) **and** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is **negative**, the participant ***is eligible*** for this protocol. If the HBV DNA test is **positive**, the participant ***is NOT eligible*** for this protocol. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this protocol. For participants who are eligible with negative HBsAg, and positive core antibody (anti-HBc) and/or surface antibody (anti-HBs), and negative HBV DNA test, HBV DNA quantitation should be monitored at least every 3 months or shorter.

These eligibility criteria based on HBV test results are also represented in:

Table 4: Eligibility based on hepatitis B virus test results

HEPATITIS B TEST RESULT			
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	**STATUS**
Negative	negative	Negative	**Eligible**
Negative	(+)	Negative	
Negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**Not eligible**
Negative	negative	(+)	**(Require testing for presence of HBV DNA*)**

* If HBV DNA is detectable, the participant is not eligible for this protocol. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol.

For participants who are not eligible for this protocol due to HBV test results, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

10.8. Appendix 8: Study Conduct During a Natural Disaster

GUIDANCE ON STUDY CONDUCT DURING COVID-19

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the eCRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of participant care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

    remote (eg, by phone/telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures eg, those related to safety monitoring/efficacy evaluation/study intervention storage and administration (including training where pertinent)

procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at home administration (including the potential for self-administration of study intervention)

laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

other procedures, eg, imaging, may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

  other relevant study data elements impacted by the pandemic should also be documented/labeled as "COVID-19-related" in CRFs and/or other study systems, as directed by detailed sponsor guidance. These may include missed/delayed/modified study visits/assessments/dosing, and instances where temporary measures such as those above are implemented.

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study Statistical Analysis Plan(s) (SAPs).

- Exclusion: a potential participant with the following features will be excluded from participating in the study protocol:

  During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection

  - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

    (i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

    AND

    (ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

- NOTES on COVID-related exclusion:

  1. If a participant is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.
  2. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities / standards of care.

- Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 4 (25 August 2022)

Overall Rationale for the Amendment: To clarify the analysis timepoint, and to add exploratory endpoints.

The changes to the protocol are described in the table below. For select changes, additions to the text are indicated by underline; deletion of text is shown in ~~strikethrough~~.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 OBJECTIVES AND END POINTS	Endpoints for the long-term efficacy of guselkumab in participant with SSc was added and modified: • Change from baseline and Week 52 in mRSS at Week 76 and Week 104 • The proportion of participants who experience worsening of mRSS at Week 76 and Week 104 • The proportion of participants achieving a score of 0.6 in American College of Rheumatology Combined Response Index in dcSSc (ACR CRISS) at Week 76 and Week 104 • Change from baseline in forced vital capacity (FVC) and percent predicted FVC at Week 76 and Week 104 • The proportion of participants who experience worsening of FVC at Week 76 and Week 104 • Change from baseline in the measured absolute diffusing capacity of the lung for carbon monoxide (DLCO) and the derived percent predicted DLCO at Week 76 and Week 104 • Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 76 and Week 104 • Change from baseline in digital ulcer counts at Week 76 and Week 104 • Change from baseline in fibrotic change assessed with high-resolution computed tomography (HRCT) at Week 76 and Week 104 in participants with baseline fibrosis/fibrotic changes • The proportion of participants who experience worsening of fibrotic change assessed with HRCT at Week 76 and Week 104 • Change from baseline in Frequency Scale for the Symptoms of Gastroesophageal reflux disease (FSSG) score at Week 76 and Week 104 Endpoints for the safety and tolerability of guselkumab in participants with SSc was modified: • Number and proportion of participants with treatment-emergent adverse events (AEs) and serious adverse events (SAEs) or adverse events of special interest (AESI) from baseline through Week 24, Week 52 ~~and~~ Week76 and Week 104	To add exploratory endpoints for LTE.
1.1 Synopsis	Endpoints for to additional efficacy of guselkumab in	For Clarification

Section Number and Name	Description of Change	Brief Rationale
3 OBJECTIVES AND END POINTS	participants with SSc was modified: • Change from baseline in digital ulcer counts at Week 24 and Week 52 ~~in participants with digital ulcers at baseline~~	
1.3 Schedule of Activities (SoA) Table 1	The following text was modified: Autoantibodies (including, but not limited to anti-RNA polymerase, anti-centromere, and anti-topoisomerase)[j]	For clarification.
7.1 Discontinuation of Study intervention	The following text was modified: • The participant initiates treatment with prohibited therapies listed in Section 6.8 unless agreed upon with the sponsor medical monitor.	For clarification.
8.8 Autoantibodies	The following text was modified: Samples will be collected at screening (see Section 1.3), to evaluate the presence of autoantibodies (including, but not limited to anti-RNA polymerase, anti-centromere, and anti-topoisomerase).	For clarification.
9.4.1 General Considerations	The following text was added: The primary analysis will be performed when all participants have completed the Week 24 visit or discontinued earlier. The final analysis will be performed when all participants have completed the last study visit or discontinued earlier. Other analysis timepoints are described in Section 9.4.6.	To clarify the timing of primary analysis and final analysis.
9.4.6 Other Analysis Interim Analysis	The following text was modified: ~~No interim analysis is planned.~~ The primary analysis will be performed when all participants have completed Week 24 or discontinued earlier. Internal Decision committee (IDC) will determine whether the LTE can continue or not based on the primary analysis results. In addition, selected sponsor personnel will be unblinded at the primary analysis for internal decision-making. Details of the unblinding will be specified in SAP. If LTE continues, an interim analysis will be performed when all participants have completed Week 52 or discontinued earlier. All sponsor personnel will be unblinded at the analyses for internal decision-making and/or interactions with health authorities.	To clarify the analysis timepoints during the study.

Amendment 3 (30 September 2021)

Overall Rationale for the Amendment: To add long-term extension (LTE) and Self-administration of study intervention.

The changes to the protocol are described in the table below. For select changes, additions to the text are indicated by underline; deletion of text is shown in ~~strikethrough~~.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis OBJECTIVES AND ENDPOINTS 3 OBJECTIVES AND ENDPOINTS	The following text was modified: Secondary Endpoint: • Number and proportion of participants with treatment-emergent adverse events (AEs) and serious adverse events (SAEs) or adverse events of special interest (AESI) from baseline through Week 24,	LTE was added to evaluate the long- term safety of guselkumab in systemic sclerosis participants. In addition, efficacy will be

Section Number and Name	Description of Change	Brief Rationale
	Week 52 and Week ~~52~~ 104. Additional Exploratory Objectives and Endpoints were added: Objectives: To evaluate the long-term efficacy of guselkumab in participant with SSc Endpoints: • Change from baseline in mRSS at Week 104 • The proportion of participants who experience worsening of mRSS at Week 104 • The proportion of participants achieving a score of 0.6 in American College of Rheumatology Combined Response Index in dcSSc (ACR CRISS) at Week 104 • Change from baseline in forced vital capacity (FVC) and percent predicted FVC at Week 104 • Change from baseline in the measured absolute diffusing capacity of the lung for carbon monoxide (DLCO) and the derived percent predicted DLCO at Week 104	evaluated for exploratory purpose.
1.1 Synopsis OVERALL DESIGN 4.1 Overall Design	The following text was modified: The main study will be conducted in 3 phases: a maximum 6-week screening phase, a 52-week double blind intervention phase, and a safety follow-up phase with a post-intervention follow-up visit at 12 weeks after the participant's last dose of study intervention to collect any AEs since the last study visit. ~~The duration of individual participation will be approximately 66 weeks. Two planned database locks (DBLs) will occur when all participants complete the Week 24 visit and Week 60 visit (safety follow-up).~~ Participants who complete the main study (Week 0 through 52: ie, after the Week 48 evaluation, prior to Week 52 evaluation) and who, in the opinion of the investigator, may benefit from continued treatment, will participate in the LTE by signing the ICF before or at Week 52. The duration of individual participation will be approximately 66 weeks without LTE and 118 weeks with LTE. Three planned database locks (DBLs) will occur: when all participants complete the Week 24 visit (hereinafter referred to as "Week 24 DBL"), EOS of the main study (Week 52 visit for participants who entered LTE or Week 60 visit for participants who did not enter LTE, hereinafter referred to as "Week 52 DBL"), and EOS of LTE (Week 112 visit, hereinafter referred to as "Final DBL"). Of note: if the LTE is terminated as per the IDC's (Internal Decision Committee) recommendation (Section 9.5), there will be 2 DBLs (Week 24 and Week 52 DBLs) only and the LTE data collected for the participants who already entered LTE at the time of Week 24 DBL will be analyzed at Week 52 DBL, along with the data through Week 52 or 60 visit.	
1.1 Synopsis INTERVENTION	The following text was added: During the LTE, all participants will receive	

Section Number and Name	Description of Change	Brief Rationale
GROUPS AND DURATION	guselkumab treatment in LTE as below depending on the arms they were in the main study: • Group/Arm A (guselkumab arm from the main study): Guselkumab 200 mg SC and placebo IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100. • Group/Arm B (placebo arm from the main study): Placebo SC and guselkumab 400 mg IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100. The following text was modified: The duration of individual participation will be approximately 66 weeks without LTE and 118 weeks with LTE.	
1.2 Schema	Figure 1 was modified. Figure 2: Schematic Overview of LTE was added.	
1.3 Schedule of Activities, Table 1	The following text was added/modified: -Title: Schedule of Activities (SoA) of Screening and Double-Blind Study Intervention (Main Study) -Footnotes: n. For participants who will NOT enter LTE, refer to Week 52 in Table 1. For participants who will enter LTE, refer to Week 52 and the subsequent visits in Table 2. o. Only participants who will NOT enter LTE should perform the safety follow up visit at Week 60. p. ICF for participation of LTE should be obtained at the latest at Week 52. ICF for participation of LTE was added at Week 48 Following was added in Abbreviations: LTE= long-term extension	
1.3 Schedule of Activities, Table 2	Schedule of activities table (Table 2) was added for Long-Term Extension for Eligible Participants Who Have Completed the Main Study (LTE).	
4.1 Overall Design	The following text was added: For the main study, participants will be randomly assigned in a 1:1 ratio, based on randomization strata of presence of ILD (yes, no), baseline mRSS (low [≥10 to ≤15] or high [≥16 to ≤22]), and baseline anti topoisomerase I antibody status (positive, negative), to 1 of the following treatment groups: The detail is provided in Section 4.1.1 Long-term Extension. During the LTE, Self-Administration will be allowed for participants who complete training. Refer to Section 4.1.2 Self-Administration of Study Intervention.	
4.1.1 Long-term Extension	New section was added: The objective of LTE is to evaluate the long-term safety and efficacy of guselkumab in SSc patients. The LTE	

Section Number and Name	Description of Change	Brief Rationale
	begins with the completion of the assessments at the Week 52, and LTE continues through LTE Week 104. The LTE includes a safety follow-up phase with a post-intervention follow-up visit at LTE Week 112 (12 weeks after the participant's last dose of study intervention). Participants who complete the main study and who, in the opinion of the investigator, may benefit from continued treatment, will participate in the LTE by signing the ICF before or at Week 52, will receive guselkumab treatment in LTE as below depending on the arms they were in the main study (Week 0 through 52). • Group/Arm A (guselkumab arm from the main study): Guselkumab 200 mg SC and placebo IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100. • Group/Arm B (placebo arm from the main study): Placebo SC and guselkumab 400 mg IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100. During the LTE, all protocol-allowed concomitant medications and rescue medications may be administered at the discretion of the investigator. Prohibited medications listed in Section 6.1 continue to be prohibited in the LTE. All study evaluations to be performed during the LTE are listed in the Section 1.3 Schedule of Activities (SoA). The study blind will be maintained until the Week 52 DBL and participants will continue to receive study intervention in a blinded manner at all visits until that time. The Final DBL will occur when all participants complete the LTE (EOS for LTE period). An internal decision committee (IDC) will be established to determine whether the LTE can continue or not based on the data from Week 24 DBL, as a risk mitigation if few benefits of guselkumab has been observed (Section 9.5). The decision will be informed to investigators by sponsor's study site monitor, only if LTE is terminated. Investigators must inform all participants to take the following actions; • Participants who have already entered LTE will discontinue study intervention, and perform Early termination visit and safety follow-up visit (Week 112) as per Section 1.3. • Participants who are still in the main study will continue study intervention until Week 52, and follow-up visit (Week 60) to complete the study as per Section 1.3, unless there is any safety concern. • If the termination decision is made for safety concern, then all participants will be discontinued from both LTE and main study. At selected visits during the LTE, at the discretion of	

Section Number and Name	Description of Change	Brief Rationale
	the investigator and participant, and after appropriate and documented training, participants will self-administer study intervention. Details are provided in Section 4.1.2 Self-Administration of Study Intervention. A diagram of the study design is provided in Section 1.2. Schema.	
4.2.1 Study-specific Ethical Design Considerations	The following text was modified: The total blood volume to be collected (up to 413 mL per participant through Week 52, and up to 567 mL per participant through Week 112) is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the blood donation rule by the Japanese Red Cross Society.	
4.4 End of Study Definition Study Completion Definition	The following text was modified: A participant who will not enter LTE will be considered to have completed the main study if he or she has completed all the assessments at Week 52 of the double-blind phase and completed the final safety follow-up visit (EOS). A participant who will enter LTE will be considered to have completed the main study if he or she has completed all the assessments at Week 52 of the double-blind phase, and the participant will be considered to have completed the LTE study if he or she has completed all the assessments at LTE Week 104 and completed the final safety follow-up visit (LTE-EOS). Participants who prematurely discontinue study intervention for any reason before completion of the double-blind phase and LTE can be considered to have completed the study if they have completed all the assessments at early termination visit and completed the final safety follow-up visit.	
6.1 Study Intervention(s) Administered	The following text was added: During the LTE, participants will receive guselkumab treatment in LTE as below depending on the arms they were in the main study: • Group/Arm A (guselkumab arm from the main study) : Guselkumab 200 mg SC and placebo IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100. • Group/Arm B (placebo arm from the main study): Placebo SC and guselkumab 400 mg IV at LTE Weeks 52, 56, and 60 followed by guselkumab 200 mg SC Q4W from LTE Week 64 until Week 100. After Week 68 participants who have been appropriately trained in the self-administration of study intervention may self-administer study intervention. At-home administration is allowed for selected visits. More details are provided in Section 4.1.2 Self-Administration of Study Intervention.	
6.3 Measures to Minimize Bias: Randomization and	The following text was modified: Under normal circumstances, the blind should not be	

Section Number and Name	Description of Change	Brief Rationale
Blinding Blinding	broken until ~~all participants have completed the study and the Week 60 database is finalized.~~the Week 52 DBL. However, selected sponsor personnel will be unblinded for analysis after the Week 24 DBL has occurred. All site personnel and participants will remain blinded to the treatment assignments until the~~ last participant completes Week 60 evaluations and the database has been locked.~~Week 52 DBL. An unblinding plan will be developed and finalized prior to any unblinding to designate sponsor personnel who will have access to the unblinded data during the period from the Week 24 DBL to the Week~~ 60~~52 DBL. An internal decision committee (IDC) will be established to determine whether the LTE can continue or not with the data from Week 24 DBL and the IDC member will be unblinded to all Week 24 data to facilitate the decision making (Section 9.5).	
6.6 Continued Access to Study Intervention After the End of the Study	The following text was modified: This protocol is designed to provide participants with up to approximately ~~52~~104 weeks of treatment, including LTE.	
8 STUDY ASSESSMENTS AND PROCEDURES Overview	The following text was modified: For each participant, the maximum amount of blood drawn ~~from each participant~~ in this study will not exceed ~~413~~ 567 mL through Week 112. Table 3: Volume of Blood to be Collected from Each Participant was updated as per Table 1 and 2.	
8.2.2 Vital Signs	The following text was modified: Through Week ~~52~~ 112, vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained before and approximately every 30 minutes during every IV infusion, and for 1 hour at approximately 30-minute intervals after completion of the final IV infusion.	

Section Number and Name	Description of Change	Brief Rationale
9.5 Internal Decision Committee	New section was added: An Internal Decision Committee (IDC), composed of sponsor management representatives from Clinical Science TA, Clinical Science Physician, Safety Physician and Biostatistics who are not associated with study conduct, will be responsible for deciding whether to continue the LTE until its planned end based on the overall benefit-risk profile as obtained at the Week 24 DBL. The IDC will have access to all unblinded safety and efficacy summary tables/figures and listings produced for Week 24 DBL. Only if it is judged by IDC that the benefit of continuing guselkumab until the end of LTE outweighs its risk, the LTE will continue until LTE Week 112 as planned (Section 4.1.1). Otherwise, the LTE will be terminated and the decision will be communicated to investigators immediately. The membership of this IDC, the analyses to be performed at Week 24 DBL, the prespecified decision criteria, and the decision communication flow chart will be provided in SAP in greater details.	To determine Go or No-Go of LTE. The No-Go criteria will be prespecified in the SAP, ahead of the Week 24 DBL.
4.1.2 Self-Administration of Study Intervention	New section was added: From the LTE, all participants who are willing to perform self-study intervention administration can receive training on how to self-administer study intervention at the investigative site. Three times trainings are required, and participants can start the training at any time after Week 56. At-home administration can begin from the selected visit according to regional/local regulations and instruction at the discretion of the investigator and participant, and upon completion of training. Participants who are eligible for self-intervention administration will be supplied with study intervention for at-home administration at Week 80 and will have the first at-home administration at Week 84. At-home administration can only be performed for the following visits (if applicable): LTE Weeks 84, 92, and 100. Participants will record all at-home study intervention administrations on a diary card. Participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or bleeding. Finally, participants will continue to have study visits and assessments at the investigative sites through LTE, as outlined in Section 1.3. Participants who are unable or unwilling to have injections administered away from the site will be required to return to the site for administration of study intervention.	Self-administration (including at home administration) was added as an option in LTE to obtain the data of self-administration with guselkumab.
6.2 Preparation/ Handling/Storage/ Accountability Preparation/Handling/Storage	The following text was added: Study personnel will instruct participants on how to transport, store, and administer study intervention for at-home use during the LTE as indicated for this protocol.	
6.2 Preparation/ Handling/Storage/	The following text was added: Participants who will be self-administering study	

Section Number and Name	Description of Change	Brief Rationale
Accountability Accountability	intervention at home will receive detailed instructions for study intervention storage and disposal of used syringes and handling of unused study material. These participants will receive a sharps container to dispose of used syringed and will be instructed to return the sharps container and/or unused cartons with syringes. Participants who self-administer at home will record study intervention administrations with time and date information on a diary card.	
8 STUDY ASSESSMENTS AND PROCEDURES Study-specific Materials	The following supplies were added: • Instruction for use of prefilled syringe for site staff • Instruction for use of prefilled syringe for subjects • Subject diary for at home administration / self-administration	
1.1 Synopsis OBJECTIVES AND ENDPOINTS 3 OBJECTIVES AND ENDPOINTS	The following text were modified: Secondary Objectives: To evaluate the additional efficacy of guselkumab in participants with SSc Exploratory Objectives: To evaluate the other efficacy of guselkumab in participants with SSc To evaluate the effect of guselkumab vs placebo on the pharmacodynamic (PD) and SSc disease biomarkers ~~gain insights into SSc disease biology and the role of the IL-23 pathway in SSc~~ Exploratory Endpoints: • Change from ~~B~~baseline ~~levels of and treatment changes in~~ levels of skin (optional) and ~~blood cellular and molecular~~ circulating (blood cellular based) biomarkers over time to enable:	For clarification.
1.1 Synopsis IMMUNOGENICITY EVALUATIONS	The following text was added: Autoantibodies Samples will be collected at screening to evaluate the presence of autoantibodies (including, but not limited to anti-ribonucleic acid [RNA] polymerase, anti-centromere, and anti-topoisomerase).	For clarification.
1.3 Schedule of Activities, Table 1	The following footnotes were modified: h. Screening should occur within 6 weeks prior to W0 visit. The study visit week are indicated and calculated based on the day of randomization/first administration of the study intervention (W0 visit). Visit window should be ±7 days for each visit. (Visit window for W0 visit should be -7 days). i. Pulmonary function tests include forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). If decline in ~~FVC~~% predicted FVC ≥ 15 % (relative) is seen, another FVC test needs to be performed within a month.	For clarification.
5.2 Exclusion Criteria	The following text was modified: Prior/Concomitant Therapy 22: • Has received therapy within 12 weeks, or 5 half-lives (whichever is longer): Systemic and topical Janus kinase inhibitor (eg, tofacitinib, upadacitinib)	For clarification to be consistent with inclusion criteria and prohibited medications.

Section Number and Name	Description of Change	Brief Rationale
	Prior/Concomitant Therapy 23: • Within 6 weeks of first study intervention: Systemic immunosuppressive agents (including but not limited to cyclosporine A, azathioprine, tacrolimus, sirolimus, sulfasalazine, leflunomide with cholestyramine washout or mycophenolate mofetil/mycophenolic acid)	
6.8 Concomitant Therapy Prohibited and restricted therapies	The following text was modified: • Systemic immunosuppressive agents (including but not limited to cyclosporine A, azathioprine, tacrolimus, sirolimus, methotrexate, sulfasalazine, leflunomide with cholestyramine washout or mycophenolate mofetil/mycophenolic acid) • Systemic and topical Janus kinase inhibitors (eg, tofacitinib, upadacitinib)	For clarification to be consistent with inclusion and exclusion criteria.
8.1.2 American College of Rheumatology Combined Response Index in Diffuse Cutaneous Systemic Sclerosis Score	The following text was modified: For the remaining participants, calculate the probability based on change in 5 measures: mRSS, % of predicted FVC ~~%,~~ HAQ-DI, patient's global assessment, and physician's global assessment, where each measure has a probability score between 0 and 1 (Khanna 2016b). ACR CRISS sore will be calculated by the sponsor.	For clarification.
8.1.5 Patient-reported Outcomes Health Assessment Questionnaire -Disability Index	The following text was modified: The Stanford HAQ translated into Japanese ~~(original HAQ) and a Japanese version of the HAQ (J HAQ)~~ with culturally appropriate modifications of the arising, eating, and reach category questions will be used in the study~~. The J HAQ includes 20 original and 3 modified questions. The HAQ disability index (HAQ-DI) score will be calculated in 2 ways. First, the 20 original questions are used to calculate the original HAQ score. Then the 17 original and 3 modified questions are used to calculate a J HAQ score~~ (Matsuda 2003).	Corrected factually inaccurate description
8.6 Biomarkers	The following text was added: Data collected from these samples will be used for exploratory research that will include, but are not limited to, the following objectives: • To understand the molecular effects of guselkumab. • To understand SSc pathogenesis. • To understand why individual participants may respond differently to guselkumab. • To understand the impact of treatment with guselkumab on skin or systemic inflammation. • To develop diagnostic tests to identify SSc or SSc populations that may be responsive or nonresponsive to treatment with guselkumab.	For clarification.

Amendment 2 (20 May 2021)

Overall Rationale for the Amendment: To modify assessments on Schedule of Activities.

The changes to the protocol are described in the table below. The deletion of text is shown in ~~strikethrough~~.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities, Table 1	Of the following timing of efficacy assessments, Weeks 8, 16, 32 and 40 were deleted, and Week 12 and 36 were added. • Physician's global assessment • Patient's global assessment • HAQ-DI • FSSG	Changed in line with the timing of ACR CRISS at Week 12 because these assessments are required for ACR CRISS. Subsequently, the assessment interval was set to every 12 weeks.
1.3 Schedule of Activities, Table 1	Timing of mRSS assessment was changed to every 4 weeks.	Increased the frequency of primary endpoint assessment.
1.3 Schedule of Activities, Table 1	The following safety assessments were added to the Early Termination Visit (ET). •Weight •12-lead ECG	Absent by mistake.
1.3 Schedule of Activities, Table 1	Separate blood sample collection for Pharmacogenomics into Blood sample collection for DNA (EDTA tube) and Blood sample collection for RNA (PAXgene tube) according to the collection timing. And following footnote was modified. d. The pharmacogenomic sample should be collected at the specified time points ~~(EDTA tube sample for DNA at Week 0 and Paxgene tube samples for RNA at Week 0, 4, and 24)~~, but it may be collected at a later time point without constituting a protocol deviation.	For clarification.

Amendment 1 (25 March 2021)

Overall Rationale for the Amendment: To add rescue therapy and modify endpoints.

The changes to the protocol are described in the table below. For select changes, additions to the text are indicated by underline; deletion of text is shown in ~~strikethrough~~.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, SAFETY EVALUATIONS	The following text was deleted: Safety evaluations conducted at each study visit will include the assessment of AEs (at the visit and those occurring between evaluation visits), ILD monitoring (assessed by centrally read HRCT), TB evaluation and other infection assessments, clinical laboratory blood tests (hematology and serum chemistry including C-reactive protein), pregnancy testing, ~~suicidal ideation and behavior risk monitoring,~~ physical examinations, ECG measurements, vital signs (as defined in the Schedule of Activities), concomitant medication review, and observations for injection-site reactions, hypersensitivity reactions, and AEs temporally associated with an infusion.	Added by mistake
1.1 Synopsis, OBJECTIVES AND ENDPOINTS, 3 Objectives and Endpoints	The following text was modified: Secondary Endpoint: • Change from baseline in forced vital capacity (FVC) and percent predicted FVC~~forced vital capacity (FVC)~~ at Week 24 and Week 52 • Change from baseline in the measured absolute	Major secondary endpoint and exploratory endpoint were modified. Endpoint of DLCO was moved to secondary endpoint from

Section Number and Name	Description of Change	Brief Rationale
	diffusing capacity of the lung for carbon monoxide (DLCO) and the derived percent predicted DLCO at Week 24 and Week 52 Exploratory Endpoint: • The proportion of participants who experience worsening of ~~percent predicted~~ FVC at Week 24 and Week 52 The following text was deleted: Exploratory Endpoint: ~~• Change from baseline in the measured absolute diffusing capacity of the lung for carbon monoxide (DLCO) and the derived percent predicted DLCO at Week 24 and Week 52~~	exploratory endpoint to evaluate pulmonary test as secondary (FVC and DLCO).
1.1 Synopsis, OVERALL DESIGN 4.1 Overall Design	The following text was added: Two planned database locks (DBLs) will occur when all participants complete the Week 24 visit and Week 60 visit (safety follow-up).	DBL timepoints were added for clarification.
1.1 Synopsis, OVERALL DESIGN, 4.1 Overall Design, 8.1 Efficacy Assessments, 8.1.3 Pulmonary Function Tests	The following text was modified: DLCO unit was changed from mmol/min/kPa to ml/min/mm Hg. DLCO (ml/min/mm Hg)	DLCO unit was changed for clarification.
1.3 Schedule of Activities, Table 1	ACR CRISS timepoints were added at screening, week 12, 24, 52, and early termination visits.	Clarification on when and how ACR CRISS score will be calculated was updated.
8.1.2 American College of Rheumatology Combined Response Index in Diffuse Cutaneous Systemic Sclerosis Score	The following text was modified: Application of ACR CRISS algorithm in a randomized clinical trial is a 2-step process. Firstly, evaluate if participants have met the criterion for not-improved. If yes, these participants are assigned a probability score of 0.0. Investigators will evaluate if the participants have met the criterion: • New scleroderma renal crisis • Decline in FVC % predicted ≥15% (relative), confirmed by another FVC test within a month, HRCT to confirm ILD (if previous HRCT of chest did not show ILD) and FVC <80% of predicted* • New onset of left ventricular failure (defined as left ventricular ejection fraction ≤45%) requiring treatment* • New onset of PAH on right-sided heart catheterization requiring treatment* * Attributable to systemic sclerosis For the remaining participants, calculate the probability based on change in 5 measures: mRSS, FVC %, HAQ-DI, patient's global assessment, and physician's global assessment, where each measure has a probability score between 0 and 1 (Khanna 2016b). ACR CRISS sore will be calculated by the	

Section Number and Name	Description of Change	Brief Rationale
	sponsor.	
1.3 Schedule of Activities, Table 1	Pulmonary function test was deleted from Week 36 and added for early termination visit. Weight was added at Week 12, 24 and 52.	Data timepoints were added/deleted to appropriate timing.
8.2.1 Physical Examinations	The following text was modified: Height and weight of the participants will be measured at specified visits ~~screening~~.	
5.1 Inclusion Criteria 12	The following text was modified: f. Aspartate aminotransferase (AST) ≤~~3~~ 2 × ULN g. Alanine aminotransferase (ALT) ≤~~3~~ 2 × ULN ~~*For ALT/AST values >2 upper limit of normal (ULN) participants can only be included if bilirubin is normal.~~	Inclusion criteria was updated to include appropriate population of participants, and to be consistent with the other Guselkumab trials.
5.4 Screen Failures	The following text was added: Rescreening Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.	Rescreening criteria was added for clarification.
6.3 Measures to Minimize Bias: Randomization and Blinding	The following text was modified: Under normal circumstances, the blind should not be broken until all participants have completed the study and the Week 60 database is finalized. However, selected sponsor personnel will be unblinded for analysis after the Week 24 DBL has occurred. All site personnel and participants will remain blinded to the treatment assignments until the last participant completes Week 60 evaluations and the database has been locked. An unblinding plan will be developed and finalized prior to any unblinding to designate sponsor personnel who will have access to the unblinded data during the period from the Week 24 DBL to the Week 60 DBL.	Text for unblind/blind status for analysis after Week 24 DBL was added for clarification.
6.8 Concomitant Therapy	The following text was added: Rescue Medication In the event that a participant experiences worsening criteria (Criteria: increase from baseline ≥5 in mRSS), investigators will have the option to treat with protocol-allowed rescue therapy after Week 24. - Oral Corticosteroid ≤20 mg/day of prednisolone or equivalent - Immunomodulator (Azathioprine), within the approved dose for SSc If rescue therapy as stipulated above fails to control SSc symptoms sufficiently, the investigator should consider discontinuing the patient from the study.	Rescue therapy was added for participants who may need it medically.
7.1 Discontinuation of Study Intervention	The following text was modified: • The investigator or sponsor believes that there are no further benefit of continuing the study for the participants.	Discontinuation of study intervention was updated for clarification.

Section Number and Name	Description of Change	Brief Rationale
	• The participant has severe liver test abnormalities that are not transient and are not explained by other etiologies. Such abnormalities would include (see Section 10.6, Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments): - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥5 × ULN. - ALT or AST ≥3 × ULN for more than 4 weeks. - ALT or AST ≥3 × ULN and cannot be monitored weekly for 4 weeks. - ALT or AST ≥3 × ULN and TBL ≥2 × ULN or international normalized ratio [INR] >1.5(INR not acceptable for participants on anticoagulants).ALT or AST ~~>~~≥3× ULN and symptoms (new or worsening) believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).	
8 Study Assessments and Procedures	The following text was modified: Following study specific materials were updated: • Participant recruitment materials (if needed) • CT image acquisition procedure manual and CT technologist instruction form ~~Imaging manual~~ • Capillaroscopy manual and quick reference guide • Pulmonary function test manual	Study Specific Manuals were updated.
8.1.3 Pulmonary Function Tests	The following text was added: Also, oxygen saturation data will be collected.	Collection of oxygen saturation was added for clarification
8.1.4 Physician Global Assessment	The following text was modified: PhGA rated subject's overall ~~health related to~~ SSc condition will be assessed ~~in the past 7 days~~, using a 10 cm visual analogue scale where 0 = excellent and 10 = extremely poor.	Updated to match the evaluation.
8.1.6 Digital Ulcer Assessments	The following text was modified: Ulcer counts and ulcer burden would be calculated by the sponsor.	For Clarification.
8.1.7 Nailfold Capillaroscopy	The following text was modified: The typical changes of the nailfold capillaries during SSc include the total number of capillaries, capillary dimension, capillary morphology, hemorrhages, blood flow velocity in capillaries, and length of nailfold. These changes would be calculated. Visual media will be taken. (Smith 2020; Smith 2010; Smith 2012). For details, refer to the manual. ~~presence of enlarged or giant capillaries, hemorrhages, loss of capillaries, disorganization of the microvascular array, and capillary ramifications. Reliability of semi-qualitative rating of nailfold capillaroscopy has been investigated in a previous study and the scores~~	Updated to match the evaluation.

Section Number and Name	Description of Change	Brief Rationale
	~~have value in predicting the occurrence of organ involvement and mortality in SSc (Smith 2020; Smith 2010; Smith 2012).~~	
8.1.8 High-resolution Computed Tomography (HRCT) Assessment	The following text was modified: Texture-based analysis and computer vision-based approaches can be applied to imaging data, and used to evaluate the extent of lung fibrosis in chest CT images (Weatherley 2019). This assessment should be done at central. For details on HRCT, refer to CT technologist instruction form. ~~Quantitative lung fibrosis (QLF) scoring is an objective quantitative tool to evaluate the extent of lung fibrosis in chest CT images (Kim 2010). It has shown consistent treatment efficacy results with other outcome measures in clinical trial of SSc-related ILD (Kim 2011).~~	Updated to match the evaluation.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	The text below was added: Possible Hy's law case (AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN or INR > 1.5) is considered an important medical event and must be reported to the sponsor in an expedited manner using the Serious Adverse Event Form, even before all other possible causes of liver injury have been excluded. (INR criterion is not applicable to participants receiving anticoagulants.)	Added in order to obtain information on possible Hy's law case.
8.7 Immunogenicity Assessments	The following text was deleted: ~~Serum samples will be used to evaluate the immunogenicity of anti-guselkumab antibodies.~~ Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.	Deleted duplicated sentence.
10.5 Appendix 5: Contraceptive and Barrier Guidance, Examples of Contraceptives	The following were deleted: ~~• Diaphragm~~ ~~• A combination of male condom with diaphragm (double barrier method)~~	Deleted as diaphragm is not approved for contraception.in Japan.
1.1 Synopsis, STATISTICAL METHODS, Sample Size Determination	The following text was modified: A 95% confidence interval (CI) of [−4.7, −1.7] in mRSS change from baseline to 6 months is considered a clinically meaningful change. The lower bound of this 95% CI, -4.7, has been taken as the expected ~~effect size~~ treatment difference in the sample size calculation of this study, assuming guselkumab can achieve a clinically meaningful change in most of guselkumab-treated participants	For Clarification.
1.1 Synopsis, STATISTICAL METHODS, Efficacy Analysis	The following text was modified: The p-values for the LS mean differences along with the 2-sided 80% CI ~~95%Cis~~ will be presented.	
1.1 Synopsis, STATISTICAL METHODS, Biomarkers Analyses	The following text was modified: If feasible, a non-lesional (unaffected) skin sample will be collected at Week 0; lesional (at Week 0) samples to be collected at both Weeks 0 and 24.	

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis, Hypothesis, 3 Objectives and Endpoints, HYPOTHESIS 9 Statistical Considerations, 9.1 Statistical Hypotheses	The following text was modified: Due to the PoC nature of this study, a 2-sided alpha of 0.2 is allocated for testing this PoC hypothesis. The PoC objective will be considered met if the calculated p-value for testing this PoC hypothesis is less than ~~or equal to~~ 0.2.	
1.3 Schedule of Activities, Table 1	The following was added and modified as footnote: c. All PRO assessments should be conducted before other assessments in the order listed in the above SoA table. d. The pharmacogenomic ~~(DNA)~~ sample should be collected at the specified time points (EDTA tube sample for DNA at Week 0 and Paxgene tube samples for RNA at Week 0, 4, and 24), but it may be collected at a later time point without constituting a protocol deviation. i. Pulmonary function tests include forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). If decline in FVC% predicted ≥15% (relative) is seen, another FVC test needs to be performed within a month. k. Participants with potential active tuberculosis need to pause the study intervention administration until the tuberculosis assessment is completed. l. For participants with stent, HRCT cannot be centrally read. m. For screening, information on ACR CRISS step 1 will be collected as SSc Condition of Interest.	
4.1 Overall Design 8.6 Biomarkers	The following text was modified: An optional biomarker sub-study will obtain a biopsy sample of non-lesional (unaffected) skin sample at Week 0, and lesional (at Week 0) skin at Week 0 and 24 from all participants who consent.	
5.1 Inclusion Criteria 18	The following text was modified: Male participants must agree to the following during the ~~intervention period~~ study and for at least 12 weeks after the last dose of study intervention:	
8 Study Assessments and Procedures, Table 2	The following text was modified: b. A blood sample will be collected only from participants who have consented to provide an optional DNA and RNA samples for research.	
8.2.5 Interstitial Lung Disease Monitoring	The following text was modified: The presence of ILD must be evaluated at screening using chest x-ray~~,~~/lung HRCT ~~(centrally read)~~, and/or PFTs (FVC and DLCO). All participants must be monitored with lung HRCT ~~(centrally read)~~, and/or PFTs (FVC and DLCO) as	

Section Number and Name	Description of Change	Brief Rationale
	scheduled in Section 1.3 during the study.	
8.4.3 Pharmacokinetic Parameters and Evaluations	The following text was modified: Based on the individual serum ~~plasma~~ concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of guselkumab may be derived using population PK modeling. The following was added for pharmacokinetic/pharmacodynamic evaluations: Details will be given in a population PK/PD analysis plan if explored.	
9 Statistical Considerations, 9.2 Sample Size Determination	The following text was modified: The lower bound of this 95% CI, -4.7, has been taken as the expected ~~effect size~~ treatment difference in the sample size calculation of this study, assuming guselkumab can achieve a clinically meaningful change in most of guselkumab-treated participants.	
9 Statistical Considerations, 9.4.2 Primary Endpoint	The following text was modified: The p-values for the LS mean differences along with the 2-sided ~~95% CIs~~ 80% CI will be presented.	
9.4.6 Other Analyses, Biomarkers Analyses	The following text was modified: Characterization of gene expression changes in the skin during treatment would be analyzed as determined by RNA-seq at Weeks 0 and 24. If feasible, a non-lesional (unaffected) skin sample will be collected at Week 0; lesional (at Week 0) samples to be collected at both Weeks 0 and 24	
11 References	References were added and removed as necessary.	The updating of the protocol text resulted in the addition and deletion of references.
Throughout the protocol	Minor grammatical, formatting, and/or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Pharmaceutical K.K.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	15-Nov-2022 03:12:59 (GMT)	Document Approval